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(54) Title: NOVEL GENES, COMPOSITIONS, KITS, AND METHODS FOR IDENTIFICATION, ASSESSMENT, PREVENTION, AND THERAPY OF CERVICAL CANCER

(57) Abstract: The invention relates to newly discovered nucleic acid molecules and proteins associated with cervical cancer including pre-malignant conditions such as dysplasia. Compositions, kits, and methods for detecting, characterizing, preventing, and treating human cervical cancers are provided.

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NOVEL GENES, COMPOSITIONS, KITS, AND METHODS FOR IDENTIFICATION, ASSESSMENT, PREVENTION, AND THERAPY OF CERVICAL CANCER

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5 RELATED APPLICATIONS

The present application claims priority to U.S. provisional patent application serial no. 60/298,159, filed on June 13, 2001, U.S. provisional patent application serial no. 60/298,155, filed on June 13, 2001, and U.S. provisional patent application serial no. 60/335,936, filed on November 14, 2001, all of which are expressly incorporated by reference.

FIELD OF THE INVENTION

The field of the invention is cervical cancer, including diagnosis, characterization, management, and therapy of cervical cancer.

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BACKGROUND OF THE INVENTION

The increased number of cancer cases reported in the United States, and, indeed, around the world, is a major concern. Currently there are only a handful of treatments available for specific types of cancer, and these provide no absolute guarantee of success. In order to be most effective, these treatments require not only an early detection of the malignancy, but a reliable assessment of the severity of the malignancy.

Cancer of the cervix is one of the most common malignancies in women and remains a significant public health problem throughout the world. In the United States alone, invasive cervical cancer accounts for approximately 19% of all gynecological cancers. In 1996, it was estimated that there were 14,700 newly diagnosed cases and 4900 deaths attributed to this disease (American Cancer Society, Cancer Facts & Figures 1996, Atlanta, Ga.: American Cancer Society, 1996). In many developing countries, where mass screening programs are not widely available, the clinical problem is more serious. Worldwide, the number of new cases is estimated to be 471,000 with a four-year survival rate of only 40% (Munoz et al., 1989, *Epidemiology of Cervical Cancer* In: "Human Papillomavirus", New York, Oxford Press, pp 9-39; National Institutes of Health, Consensus Development Conference Statement on Cervical Cancer, Apr.1-3, 1996).

The precursor to cervical cancer is dysplasia, also known in the art as cervical intraepithelial neoplasia (CIN) or squamous intraepithelial lesions (SIL). While it is not understood how normal cells become transformed, the concept of a continuous spectrum of histopathological change from normal, stratified epithelium through CIN to invasive cancer has been widely accepted for many years. A large body of epidemiological and molecular biological evidence has established human papillomavirus (HPV) infection as a causative factor in cervical cancer. HPV is found in 85% or more of squamous cell invasive lesions, which represent the most common histologic type seen in cervical carcinoma. Additional cofactors have also been identified, including oncogenes that have been activated by point mutations and chromosomal translocations or deletions.

In light of this, cervical cancer remains a highly preventable form of cancer when pre-invasive lesions are detected early. Cytological examination of Papanicolaou-stained cervical smears (also referred to as Pap smears) is currently the principle method for detecting cervical cancer. Not surprisingly, the effectiveness of Pap smear screening varies depending not only upon the quality of the sample being used, but also upon subjective parameters that are inherent to the analysis. In addition, despite the historical success of the test, concerns have arisen regarding its ability to reliably predict the behavior of some pre-invasive lesions (Ostor *et al.*, 1993, *Int. J. Gynecol. Pathol.* 12: 186-192; and Genest *et al.*, 1993, *Human Pathol.* 24: 730-736).

SUMMARY OF THE INVENTION

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The invention relates to cancer markers (hereinafter "markers" or "markers of the inventions"), which are listed in Table 1. The invention provides nucleic acids and proteins that are encoded by or correspond to the markers (hereinafter "marker nucleic acids" and "marker proteins," respectively). Table 1 provides the sequence identifiers of the sequences of such marker nucleic acids and proteins listed in the accompanying Sequence Listing. The invention further provides antibodies, antibody derivatives and antibody fragments which bind specifically with such proteins and/or fragments of the proteins.

The invention also relates to various methods, reagents and kits for diagnosing, staging, prognosing, monitoring and treating cervical cancer. "Cervical cancer" as used herein includes carcinomas, (e.g., carcinoma in situ, invasive

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carcinoma, metastatic carcinoma) and pre-malignant conditions, (e.g., dysplasia, including CIN or SIL). In one embodiment, the invention provides a diagnostic method of assessing whether a patient has cervical cancer or has higher than normal risk for developing cervical cancer, comprising the steps of comparing the level of expression of a marker of the invention in a patient sample and the normal level of expression of the marker in a control, e.g., a sample from a patient without cervical cancer. A significantly higher level of expression of the marker in the patient sample as compared to the normal level is an indication that the patient is afflicted with cervical cancer or has higher than normal risk for developing cervical cancer.

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According to the invention, the markers are selected such that the positive predictive value of the methods of the invention is at least about 10%, preferably about 25%, more preferably about 50% and most preferably about 90%. Also preferred for use in the methods of the invention are markers that are differentially expressed, as compared to normal cervical cells, by at least two-fold in at least about 20%,more preferably about 50% and most preferably about 75% of any of the following conditions: stage 0 cervical cancer patients, stage I cervical cancer patients, stage II cervical cancer patients, grade I cervical cancer patients, grade I cervical cancer patients, grade II cervical cancer patients, squamous cell (epidermoid) cervical cancer patients, cervical adenocarcinoma patients, cervical adenosquamous carcinoma patients, small-cell cervical carcinoma patients, malignant cervical cancer patients with primary carcinomas of the cervix, patients with primary malignant lymphomas of the cervix and patients with secondary malignant lymphomas of the cervix, and all other types of cancers, malignancies and transformations associated with the cervix.

In a preferred diagnostic method of assessing whether a patient is afflicted with cervical cancer (*e.g.*, new detection ("screening"), detection of recurrence, reflex testing), the method comprises comparing:

- a) the level of expression of a marker of the invention in a patient sample, and
- b) the normal level of expression of the marker in a control non-cervical cancer sample.

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A significantly higher level of expression of the marker in the patient sample as compared to the normal level is an indication that the patient is afflicted with cervical cancer.

The invention also provides diagnostic methods for assessing the efficacy of a therapy for inhibiting cervical cancer in a patient. Such methods comprise comparing:

- a) expression of a marker of the invention in a first sample obtained from the patient prior to providing at least a portion of the therapy to the patient, and
- b) expression of the marker in a second sample obtained from the patient following provision of the portion of the therapy.

A significantly lower level of expression of the marker in the second sample relative to that in the first sample is an indication that the therapy is efficacious for inhibiting cervical cancer in the patient.

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It will be appreciated that in these methods the "therapy" may be any therapy for treating cervical cancer including, but not limited to, chemotherapy, radiation therapy, surgical removal of tumor tissue, gene therapy and biologic therapy such as the administering of antibodies and chemokines. Thus, the methods of the invention may be used to evaluate a patient before, during and after therapy, for example, to evaluate the reduction in tumor burden.

In a preferred embodiment, the diagnostic methods are directed to therapy using a chemical or biologic agent. These methods comprise comparing:

- a) expression of a marker of the invention in a first sample obtained from the patient and maintained in the presence of the chemical or biologic agent, and
- b) expression of the marker in a second sample obtained from the patient and maintained in the absence of the agent.

A significantly lower level of expression of the marker in the second sample relative to that in the first sample is an indication that the agent is efficacious for inhibiting cervical cancer, in the patient. In one embodiment, the first and second samples can be portions of a single sample obtained from the patient or portions of pooled samples obtained from the patient.

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The invention additionally provides a monitoring method for assessing the progression of cervical cancer in a patient, the method comprising:

- a) detecting in a patient sample at a first time point, the expression of a marker of the invention;
- b) repeating step a) at a subsequent time point in time; and
- c) comparing the level of expression detected in steps a) and b), and therefrom monitoring the progression of cervical cancer in the patient.

A significantly higher level of expression of the marker in the sample at the subsequent time point from that of the sample at the first time point is an indication that the cervical cancer has progressed, whereas a significantly lower level of expression is an indication that the cervical cancer has regressed.

The invention further provides a diagnostic method for determining whether cervical cancer has metastasized or is likely to metastasize in the future, the method comprising comparing:

- a) the level of expression of a marker of the invention in a patient sample, and
- b) the normal level (or non-metastatic level) of expression of the marker in a control sample.

A significantly higher level of expression in the patient sample as compared to the normal level (or non-metastatic level) is an indication that the cervical cancer has metastasized or is likely to metastasize in the future.

The invention moreover provides a test method for selecting a composition for inhibiting cervical cancer in a patient. This method comprises the steps of:

- a) obtaining a sample comprising cancer cells from the patient;
- b) separately maintaining aliquots of the sample in the presence of a plurality of test compositions;
- c) comparing expression of a marker of the invention in each of the aliquots; and
- d) selecting one of the test compositions which significantly reduces the level of expression of the marker in the aliquot containing that test composition, relative to the levels of expression of the marker in the presence of the other test compositions.

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The invention additionally provides a test method of assessing the cervical carcinogenic potential of a compound. This method comprises the steps of:

a) maintaining separate aliquots of cervical cells in the presence and absence of the compound; and

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b) comparing expression of a marker of the invention in each of the aliquots.

A significantly higher level of expression of the marker in the aliquot maintained in the presence of the compound, relative to that of the aliquot maintained in the absence of the compound, is an indication that the compound possesses cervical carcinogenic potential.

In addition, the invention further provides a method of inhibiting cervical cancer in a patient. This method comprises the steps of:

- a) obtaining a sample comprising cancer cells from the patient;
- b) separately maintaining aliquots of the sample in the presence of a plurality of compositions;
- c) comparing expression of a marker of the invention in each of the aliquots; and
- d) administering to the patient at least one of the compositions which significantly lowers the level of expression of the marker in the aliquot containing that composition, relative to the levels of expression of the marker in the presence of the other compositions.

In the aforementioned methods, the samples or patient samples comprise cells obtained from the patient. The cells may be found in a cervical smear collected, for example, by a cervical brush. In another embodiment, the sample is a body fluid. Such fluids include, for example, blood fluids, lymph, ascitic fluids, gynecological fluids, urine, and fluids collected by vaginal rinsing. In a further embodiment, the patient sample is *in vivo*.

According to the invention, the level of expression of a marker of the invention in a sample can be assessed, for example, by detecting the presence in the sample of:

• the corresponding marker protein (e.g., a protein having one of the sequences set forth as "SEQ ID NO (AAs)" in Table 1, or a fragment of the protein (e.g. by using a reagent, such as an antibody, an antibody derivative,

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an antibody fragment or single-chain antibody, which binds specifically with the protein or protein fragment)

- the corresponding marker nucleic acid (e.g. a nucleotide transcript having one of the nucleic acid sequences set forth as "SEQ ID NO (nts)" in Table 1, or a complement thereof), or a fragment of the nucleic acid (e.g. by contacting transcribed polynucleotides obtained from the sample with a substrate having affixed thereto one or more nucleic acids having the entire or a segment of the nucleic acid sequence of any of the SEQ ID NO (nts), or a complement thereof)
- a metabolite which is produced directly (*i.e.*, catalyzed) or indirectly by the corresponding marker protein.

According to the invention, any of the aforementioned methods may be performed using a plurality (e.g. 2, 3, 5, or 10 or more) of cervical cancer markers, including cervical cancer markers known in the art. In such methods, the level of expression in the sample of each of a plurality of markers, at least one of which is a marker of the invention, is compared with the normal level of expression of each of the plurality of markers in samples of the same type obtained from control humans not afflicted with cervical cancer. A significantly altered (i.e., increased or decreased as specified in the above-described methods using a single marker) level of expression in the sample of one or more markers of the invention, or some combination thereof, relative to that marker's corresponding normal or control level, is an indication that the patient is afflicted with cervical cancer. For all of the aforementioned methods, the marker(s) are preferably selected such that the positive predictive value of the method is at least about 10%.

In a further aspect, the invention provides an antibody, an antibody derivative, or an antibody fragment, which binds specifically with a marker protein (e.g., a protein having one of the amino acid sequences set forth in the Sequence Listing) or a fragment of the protein. The invention also provides methods for making such antibody, antibody derivative, and antibody fragment. Such methods may comprise immunizing a mammal with a protein or peptide comprising the entirety, or a segment of 10 or more amino acids, of a marker protein (e.g., a protein having one of the amino acid sequences set forth in the Sequence Listing), wherein the protein or peptide may be obtained from a cell or by chemical synthesis. The methods of the invention also encompass producing

monoclonal and single-chain antibodies, which would further comprise isolating splenocytes from the immunized mammal, fusing the isolated splenocytes with an immortalized cell line to form hybridomas, and screening individual hybridomas for those that produce an antibody that binds specifically with a marker protein or a fragment of the protein.

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In another aspect, the invention relates to various diagnostic and test kits. In one embodiment, the invention provides a kit for assessing whether a patient is afflicted with cervical cancer. The kit comprises a reagent for assessing expression of a marker of the invention. In another embodiment, the invention provides a kit for assessing the suitability of a chemical or biologic agent for inhibiting cervical cancer in a patient. Such a kit comprises a reagent for assessing expression of a marker of the invention, and may also comprise one or more of such agents. In a further embodiment, the invention provides kits for assessing the presence of cervical cancer cells or treating cervical cancers. Such kits comprise an antibody, an antibody derivative, or an antibody fragment, which binds specifically with a marker protein, or a fragment of the protein. Such kits may also comprise a plurality of antibodies, antibody derivatives, or antibody fragments wherein the plurality of such antibody agents binds specifically with a marker protein, or a fragment of the protein.

In an additional embodiment, the invention also provides a kit for assessing the presence of cervical cancer cells, wherein the kit comprises a nucleic acid probe that binds specifically with a marker nucleic acid or a fragment of the nucleic acid. The kit may also comprise a plurality of probes, wherein each of the probes binds specifically with a marker nucleic acid, or a fragment of the nucleic acid.

In a further aspect, the invention relates to methods for treating a patient afflicted with cervical cancer or at risk of developing cervical cancer. Such methods may comprise reducing the expression and/or interfering with the biological function of a marker of the invention. In one embodiment, the method comprises providing to the patient an antisense oligonucleotide or polynucleotide complementary to a marker nucleic acid, or a segment thereof. For example, an antisense polynucleotide may be provided to the patient through the delivery of a vector that expresses an anti-sense polynucleotide of a marker nucleic acid or a fragment thereof. In another embodiment, the method comprises providing to the patient an antibody, an antibody derivative, or antibody fragment, which binds specifically with a marker protein or a fragment of the

protein. In a preferred embodiment, the antibody, antibody derivative or antibody fragment binds specifically with a protein having one of the amino acid sequences set forth in the Sequence Listing, or a fragment of the protein.

It will be appreciated that the methods and kits of the present invention may also include known cancer markers including known cervical cancer markers. It will further be appreciated that the methods and kits may be used to identify cancers other than cervical cancer.

DETAILED DESCRIPTION OF THE INVENTION

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The invention relates to newly discovered cancer markers associated with the cancerous state of cervical cells. It has been discovered that the higher than normal level of expression of any of these markers or combination of these markers correlates with the presence of cervical cancer including pre-malignant conditions such as dysplasia, in a patient. Methods are provided for detecting the presence of cervical cancer in a sample, the absence of cervical cancer in a sample, the stage of a cervical cancer, and other characteristics of cervical cancer that are relevant to prevention, diagnosis, characterization, and therapy of cervical cancer in a patient. Methods of treating cervical cancer are also provided.

Table 1 lists the markers of the invention which are over-expressed in cervical cancer cells compared to normal (*i.e.*, non-cancerous) cervical cells and comprises markers listed in Tables 2 and 3. Table 2 lists newly-identified nucleotide and amino acid sequences. Table 3 lists newly-identified nucleotide sequences. Tables 1-3 provide the sequence listing identifiers of the cDNA sequence of a nucleotide transcript and the amino acid sequence of a protein encoded by or corresponding to each marker, as well as the location of the protein coding sequence within the cDNA sequence.

Table 1

		SEQ ID NO	SEQ ID	
Marker	Gene Name AKAP9: A kinase (PRKA) anchor protein (yotiao) 9,	(nts)	NO (AAs)	CDS
M661	variant 1	1	2	22311946
771001	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9,			22011940
M662	variant 2	3	4	22311922
	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9,			
M663	variant 3	5	6	22312000
	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9,			
M664	variant 4	7	8	22311976
B.4.4	APOL1: Apolipoprotein L-I mNA, splice variant A,		4.5	040 4004
M1	major form	9	10	2131364
M2	APOL1: Apolipoprotein L-I mNA, splice variant B, minor form	11	12	2741518
IVIZ	APOL3: apolipoprotein L, 3; TNF-inducible protein	11	12	2741316
М3	CG12-1	13	14	4181413
OV3	AQP5: Aquaporin 5	15	16	5191316
M4	BC001980: clone MGC:5618	17	18	157225
M5	BST2: Bone marrow stromal cell antigen 2	19	20	10552
M6	BTEB1: basic transcription element binding protein 1	21	22	12651999
	CD74: CD74 antigen (invariant polypeptide of major			12001000
M665	histocompatibility complex, class II antigen-associated)	23	24	8706
M7	CDC20: CDC20 cell cycle protein	25	26	451544
M8	CDKN2C: cyclin-dependent kinase inhibitor 2C, p18	27	28	12161722
	CKTSF1B1: (cysteine knot superfamily 1, BMP			12101722
M9	antagonist 1), gremlin	29	30	451544
M10	CLDN1: claudin 1	31	32	221856
M11	CLIC4: chloride intracellular channel 4	33	34	198959
M12	COL1A1: collagen, type I, alpha 1	35	36	1204514
M13	COL1A2: collagen, type I, alpha 2	37	38	1404240
M14	COL8A1: collagen, type VIII, alpha 1	39	40	12235
M15	COPA: coatomer protein complex, subunit alpha	41	42	4674141
M16	CRIP1: cysteine-rich protein 1 (intestinal)	43	44	1234
M17	CTGF: connective tissue growth factor	45	46	1461195
M18	DOC: downregulated in ovarian cancer 1	47	48	1352393
M19	EFNA1: ephrin-A1	49	50	74691
M481	EPPK1: epiplakin 1	51	52	8915286
M20	FLJ11350: hypothetical protein FLJ11350	53	54	1061047
M21	FLJ13809: hypothetical protein FLJ13809	55	56	641593
M22	FLJ20500: hypothetical protein FLJ20500	57	58	198896
M23	FLJ23399: hypothetical protein FLJ23399	59	60	
M24	FN1: Fibronectin 1, variant 1	61	62	2831770
M25	FN1: Fibronectin 1, variant 1			<12384
M482	FOSL2: FOS-like antigen 2, variant 1	· 63	64	<16988
M483	FOSL2: FOS-like antigen 2, variant 1	65 67	66	3241304
141403	FSHPRH1: FSH primary response (LRPR1, rat)	67	66	3241304
M484	homolog 1	68	69	2702540
M26	FY: Duffy blood group	70	71	4951511

M485	G1P3:interferon, alpha-inducible protein (clone IFI-6-16)	72	73	108500
M486	GW112: GW112 protein	74	75	5091072
	HSKERUV: clone 266, Human radiated keratinocyte			
M27	mRNA 266 (keratin-related protein)	76	77	<1801
M28	HSPC121: butyrate-induced transcript 1	78	79	1501271
M29	HUMCLPB: Coactosin like protein	80	81	150576
M487	hypothetical protein	82	83	588163
M30	IFI27: (interferon, alpha-inducible protein 27	84	85	55423
OV31	IFI30: interferon, gamma-inducible protein 30	86	87	41952
M31	IFITM2: interferon induced transmembrane protein 2 (1-8D)	88	89	280678
M32	IGFBP-3: insulin-like growth factor binding protein 3	90	91	1331009
M33	IL8RA: interleukin 8	92	93	75374
M34	INHBA: Inhibin, beta-1	94	95	861366
M488	ITGA3: integrin, alpha 3 (antigen CD49C, alpha 3 subunit of VLA-3 receptor), variant a	96	97	743229
M454	ITGA3: integrin, alpha 3 (antigen CD49C, alpha 3 subunit of VLA-3 receptor), variant b	98	99	743274
M35	ITGB6: integrin, beta 6	100	101	1952561
M36	KATII: L-kynurenine/alpha-aminoadipate aminotransferase	102	103	4541731
M666	KCNAB1: potassium voltage-gated channel, shaker-related subfamily, beta member 1, variant 1	104	105	891315
M667	KCNAB1: potassium voltage-gated channel, shaker- related subfamily, beta member 1, variant 2	106	107	541313
M668	KCNAB1: potassium voltage-gated channel, shaker- related subfamily, beta member 1, variant 3	108	109	281233
M37	KIAA0662: KIAA0662 protein	110	111	<12035
M38	LAMA3: Laminin, alpha-3 (nicein (150kD), (kalinin (165kD), BM600 (150kD)	112	113	15142
M39	LAMC2: laminin, gamma 2	114	115	903671
M40	LSM5: U6 snRNA-associated Sm-like protein	116	117	1276
M41	LUM: lumican	118	119	851101
M42	MACMARCKS: macrophage myristoylated alanine- rich C kinase substrate	120	121	14601
M43	MAGP: microfibrillar-associated protein 2 precursor, transcript variant 1	122	123	115666
M44	MAGP: microfibrillar-associated protein 2 precursor, transcript variant 2	124	125	100651
M45	MAPK: mitogen-activated protein kinase 1	126	127	3281410
M489	MCM6: minichromosome maintenance deficient (mis5, S. pombe) 6	128	129	622527
M46	MDK: midkine (neurite growth-promoting factor 2)	130	131	26457
M47	MGP: matrix Gla protein	132	133	47358
M48	MMP12: matrix metalloproteinase 12	134	135	131425
M49	MMP3: matrix metalloproteinase 3, stromelysin 1, progelatinase	136	137	641497
M294	MMP7: matrix metalloproteinase 7 (matrilysin, uterine), PUMP1 proteinase, variant 1	138	139	48851
OV52	MMP7: matrix metalloproteinase 7 (matrilysin, uterine), PUMP1 proteinase, variant 2	140	139	28831

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M50	MMP9: matrix metalloproteinase 9, gelatinase B, 92kD gelatinase, 92kD type IV collagenase	141	142	202143
OV68	MSLN: mesothelin, variant 1	143	144	882196
OV69	MSLN: mesothelin, variant 1	145	146	881980
OV70	MSLN: mesothelin, variant 3	147	148	881950
OV70	MSLN: mesothelin, variant 4	149	150	882172
OV71	MSLN: mesothelin, variant 5	151	152	881926
OV43	MSLN: mesothelin, variant 6	153	154	881956
OV45	MUC1: mucin 1, transmembrane, variant 1	155	156	581605
M669	MUC1: mucin 1, transmembrane, variant 1	157	158	
MOOS		157	100	743841
M51	MYBL2: v-myb avian myeloblastosis viral oncogene homolog-like 2	159	160	1282230
M52	MYH11: smooth muscle myosin heavy chain 11, isoform SM1	161	162	896007
M53	MYH11: smooth muscle myosin heavy chain 11, isoform SM2	163	164	895905
M54	NK4: natural killer cell transcript 4 , variant 1	165	166	60764
M670	NK4: natural killer cell transcript 4, variant 2	167	168	60764
M55	NP25: (neuronal protein)	169	170	50898
OV48	OPN-a (osteopontin), SPP1 (secreted phosphoprotein 1), bone sialoprotein I	171	172	1942
OV49	OPN-b (osteopontin), SPP1 (secreted phosphoprotein 1), bone sialoprotein I	173	174	88990
OV50	OPN-c (osteopontin), SPP1 (secreted phosphoprotein 1), bone sialoprotein I	175	176	1861
M56	OSF-2, osteoblast specific factor 2 (fasciclin I-like), variant 1	177	178	122522
M491	OSF-2, osteoblast specific factor 2 (fasciclin I-like), variant 2	179	180	282367
M57	PIM2: pim-2 oncogene	181	182	1861190
M58	PLAU: plasminogen activator, urokinase	183	184	771372
M59	PLK: polo (Drosophia)-like kinase	185	186	641875
M671	PNN: pinin, desmosome associated protein	187	188	312262
M60	PRG1: proteoglycan 1, secretory granule	189	190	25501
M61	PTHLH: parathyroid hormone-like hormone	191	192	304831
M62	PTN: pleiotrophin (heparin binding growth factor 8, neurite growth-promoting factor 1)	193	194	15422048
M63	RAB6KIFL: RAB6 interacting, kinesin-like (rabkinesin6)	195	196	282700
M64	RARRES3: retinoic acid receptor responder (tazarotene induced) 3	197	198	62556
M65	RBP1: retinol-binding protein 1(cellular), CRABP-I, CRBP-I	199	200	126533
M66	RGS16: Regulator of G protein signaling-16	201	202	93701
M67	S100A2: S100 calcium binding protein A2, variant 1	203	204	72362
M68	S100A2: S100 calcium binding protein A2, variant 2	205	206	41334
M69	SCYA20: small inducible cytokine subfamily A (Cys-Cys), member 20	207	208	59349
	SPARC: Osteonectin (secreted protein, acidic,		† 	T
M70	cysteine-rich)	209	210	58969
M71	STCH: stress 70 protein chaperone, microsome- associated	211	212	371452
M492	STK12: serine/ threonine kinase 12	213	214	581092

M72	TK1: thymidine kinase 1, soluble	215	216	58762
OV86	TMPRSS4: transmembrane protease, serine 4	217	218	3101623
M73	TMSB4X: thymosin, beta 4, X chromosome	219	220	78212
M74	TOP2A: topoisomerase (DNA) II alpha (170kD)	221	222	374632
M493	TPM1: tropomyosin 1 (alpha)	223	224	57911
M75	TXN: thioredoxin	225	226	64381
M76	UBCH10: ubiquitin carrier protein E2-C	227	228	41580
M77	UBD: diubiquitin	229	230	19516
M78	unnamed gene (1)	231	232	451353
M79	unnamed gene (2)	233	234	11508
M80	VATD: vacuolar proton pump delta polypeptide	235	236	166909
M81	ZWINT: ZW10 interactor	237	238	25858

Table 2

Marker	Gene Name	SEQ ID NO (nts)	SEQ ID NO (AAs)	CDS
	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9,			2231194
M661	variant 1	1	2	6
	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9,			2231192
M662	variant 2	3	4	2
	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9,			2231200
M663	variant 3	5	6	0
	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9,			2231197
M664	variant 4	7	8	6
OV68	MSLN: mesothelin, variant 1	143	144	882196
OV69	MSLN: mesothelin, variant 2	145	146	881980
OV70	MSLN: mesothelin, variant 3	147	148	881950
OV71	MSLN: mesothelin, variant 4	149	150	882172
OV72	MSLN: mesothelin, variant 5	151	152	881926
M670	NK4: natural killer cell transcript 4 , variant 2	167	168	60764
M67	S100A2: S100 calcium binding protein A2, variant 1	203	204	72362
OV86	TMPRSS4: transmembrane protease, serine 4	217	218	3101623
M78	unnamed gene (1)	231	232	451353
M79	unnamed gene (2)	233	234	11508

Table 3

Marker	Gene Name	SEQ ID NO (nts)	SEQ ID NO (AAs)	CDS
M481	EPPK1: epiplakin 1	51	52	8915286
M482	FOSL2: FOS-like antigen 2, variant 1	65	66	3241304
M483	FOSL2: FOS-like antigen 2, variant 2	67	66	3241304
M484	FSHPRH1: FSH primary response (LRPR1, rat) homolog 1	68	69	2702540
M35	ITGB6: integrin, beta 6	100	101	1952561
OV43	MSLN: mesothelin, variant 6	153	154	881956

Definitions

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As used herein, each of the following terms has the meaning associated with it in this section.

The articles "a" and "an" are used herein to refer to one or to more than one (i.e. to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

A "marker" is a gene whose altered level of expression in a tissue or cell from its expression level in normal or healthy tissue or cell is associated with a disease state, such as cancer. A "marker nucleic acid" is a nucleic acid (e.g., mRNA, cDNA) encoded by or corresponding to a marker of the invention. Such marker nucleic acids include DNA (e.g., cDNA) comprising the entire or a partial sequence of any of the nucleic acid sequences set forth in the Sequence Listing or the complement of such a sequence. The marker nucleic acids also include RNA comprising the entire or a partial sequence of any of the nucleic acid sequences set forth in the Sequence Listing or the complement of such a sequence, wherein all thymidine residues are replaced with uridine residues. A "marker protein" is a protein encoded by or corresponding to a marker of the invention. A marker protein comprises the entire or a partial sequence of any of the sequences set forth in the Sequence Listing. The terms "protein" and "polypeptide' are used interchangeably.

The term "probe" refers to any molecule which is capable of selectively binding to a specifically intended target molecule, for example, a nucleotide transcript or protein encoded by or corresponding to a marker. Probes can be either synthesized by one skilled in the art, or derived from appropriate biological preparations. For purposes of detection of the target molecule, probes may be specifically designed to be labeled, as

described herein. Examples of molecules that can be utilized as probes include, but are not limited to, RNA, DNA, proteins, antibodies, and organic molecules.

A "cervical-associated" body fluid is a fluid which, when in the body of a patient, contacts or passes through cervical cells or into which cells or proteins shed from cervical cells are capable of passing. The cells may be found in a cervical smear collected, for example, by a cervical brush. Exemplary cervical-associated body fluids include blood fluids, lymph, ascitic fluids, gynecological fluids, cystic fluid, urine, and fluids collected by vaginal rinsing.

The "normal" level of expression of a marker is the level of expression of the marker in cervical cells of a human subject or patient not afflicted with cervical cancer

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An "over-expression" or "significantly higher level of expression" of a marker refers to an expression level in a test sample that is greater than the standard error of the assay employed to assess expression, and is preferably at least twice, and more preferably three, four, five or ten times the expression level of the marker in a control sample (e.g., sample from a healthy subjects not having the marker associated disease) and preferably, the average expression level of the marker in several control samples.

A "significantly lower level of expression" of a marker refers to an expression level in a test sample that is at least twice, and more preferably three, four, five or ten times lower than the expression level of the marker in a control sample (e.g., sample from a healthy subject not having the marker associated disease) and preferably, the average expression level of the marker in several control samples.

As used herein, the term "promoter/regulatory sequence" means a nucleic acid sequence which is required for expression of a gene product operably linked to the promoter/regulatory sequence. In some instances, this sequence may be the core promoter sequence and in other instances, this sequence may also include an enhancer sequence and other regulatory elements which are required for expression of the gene product. The promoter/regulatory sequence may, for example, be one which expresses the gene product in a tissue-specific manner.

A "constitutive" promoter is a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a living human cell under most or all physiological conditions of the cell.

An "inducible" promoter is a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a living human cell substantially only when an inducer which corresponds to the promoter is present in the cell.

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A "tissue-specific" promoter is a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a living human cell substantially only if the cell is a cell of the tissue type corresponding to the promoter.

A "transcribed polynucleotide" or "nucleotide transcript" is a polynucleotide (e.g. an mRNA, hnRNA, a cDNA, or an analog of such RNA or cDNA) which is complementary to or homologous with all or a portion of a mature mRNA made by transcription of a marker of the invention and normal post-transcriptional processing (e.g. splicing), if any, of the RNA transcript, and reverse transcription of the RNA transcript.

"Complementary" refers to the broad concept of sequence complementarity between regions of two nucleic acid strands or between two regions of the same nucleic acid strand. It is known that an adenine residue of a first nucleic acid region is capable of forming specific hydrogen bonds ("base pairing") with a residue of a second nucleic acid region which is antiparallel to the first region if the residue is thymine or uracil. Similarly, it is known that a cytosine residue of a first nucleic acid strand is capable of base pairing with a residue of a second nucleic acid strand which is antiparallel to the first strand if the residue is guanine. A first region of a nucleic acid is complementary to a second region of the same or a different nucleic acid if, when the two regions are arranged in an antiparallel fashion, at least one nucleotide residue of the first region comprises a first portion and the second region comprises a second portion, whereby, when the first and second portions are arranged in an antiparallel fashion, at least about 50%, and preferably at least about 75%, at least about 90%, or at least about 95% of the nucleotide residues of the first portion are capable of base pairing

with nucleotide residues in the second portion. More preferably, all nucleotide residues of the first portion are capable of base pairing with nucleotide residues in the second portion.

"Homologous" as used herein, refers to nucleotide sequence similarity between two regions of the same nucleic acid strand or between regions of two different nucleic acid strands. When a nucleotide residue position in both regions is occupied by the same nucleotide residue, then the regions are homologous at that position. A first region is homologous to a second region if at least one nucleotide residue position of each region is occupied by the same residue. Homology between two regions is expressed in terms of the proportion of nucleotide residue positions of the two regions that are occupied by the same nucleotide residue. By way of example, a region having the nucleotide sequence 5'-ATTGCC-3' and a region having the nucleotide sequence 5'-TATGGC-3' share 50% homology. Preferably, the first region comprises a first portion and the second region comprises a second portion, whereby, at least about 50%, and preferably at least about 75%, at least about 90%, or at least about 95% of the nucleotide residue positions of each of the portions are occupied by the same nucleotide residue. More preferably, all nucleotide residue positions of each of the portions are occupied by the same nucleotide residue.

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A molecule is "fixed" or "affixed" to a substrate if it is covalently or non-covalently associated with the substrate such the substrate can be rinsed with a fluid (*e.g.* standard saline citrate, pH 7.4) without a substantial fraction of the molecule dissociating from the substrate.

As used herein, a "naturally-occurring" nucleic acid molecule refers to an RNA or DNA molecule having a nucleotide sequence that occurs in an organism found in nature.

A cancer is "inhibited" if at least one symptom of the cancer is alleviated, terminated, slowed, or prevented. As used herein, cervical cancer is also "inhibited" if recurrence or metastasis of the cancer is reduced, slowed, delayed, or prevented.

A kit is any manufacture (e.g. a package or container) comprising at least one reagent, e.g. a probe, for specifically detecting the expression of a marker of the invention. The kit may be promoted, distributed, or sold as a unit for performing the methods of the present invention.

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"Proteins of the invention" encompass marker proteins and their fragments; variant marker proteins and their fragments; peptides and polypeptides comprising an at least 15 amino acid segment of a marker or variant marker protein; and fusion proteins comprising a marker or variant marker protein, or an at least 15 amino acid segment of a marker or variant marker protein.

Unless otherwise specified herewithin, the terms "antibody" and "antibodies" broadly encompass naturally-occurring forms of antibodies (e.g., IgG, IgA, IgM, IgE) and recombinant antibodies such as single-chain antibodies, chimeric and humanized antibodies and multi-specific antibodies, as well as fragments and derivatives of all of the foregoing, which fragments and derivatives have at least an antigenic binding site. Antibody derivatives may comprise a protein or chemical moiety conjugated to an antibody.

Description

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The present invention is based, in part, on newly identified markers which are over-expressed in cervical cancer cells as compared to their expression in normal (*i.e.* non-cancerous) cervical cells. The enhanced expression of one or more of these markers in cervical cells is herein correlated with the cancerous state of the tissue. The invention provides compositions, kits, and methods for assessing the cancerous state of cervical cells (*e.g.* cells obtained from a human, cultured human cells, archived or preserved human cells and *in vivo* cells) as well as treating patients afflicted with cervical cancer.

The compositions, kits, and methods of the invention have the following uses, among others:

- 1) assessing whether a patient is afflicted with cervical cancer;
- 2) assessing the stage of cervical cancer in a human patient;
- 3) assessing the grade of cervical cancer in a patient;
- 4) assessing the benign or malignant nature of cervical cancer in a patient;
- 5) assessing the metastatic potential of cervical cancer in a patient;
 - 6) assessing the histological type of neoplasm associated with cervical cancer in a patient;

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7) making antibodies, antibody fragments or antibody derivatives that are useful for treating cervical cancer and/or assessing whether a patient is afflicted with cervical cancer;

8) assessing the presence of cervical cancer cells;

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- assessing the efficacy of one or more test compounds for inhibiting cervical cancer in a patient;
- 10) assessing the efficacy of a therapy for inhibiting cervical cancer in a patient;
- 11) monitoring the progression of cervical cancer in a patient;
- 12) selecting a composition or therapy for inhibiting cervical cancer in a patient;
- 13) treating a patient afflicted with cervical cancer;
- 14) inhibiting cervical cancer in a patient;
- assessing the cervical carcinogenic potential of a test compound; and
- 16) preventing the onset of cervical cancer in a patient at risk for developing cervical cancer.

The invention thus includes a method of assessing whether a patient is afflicted with cervical cancer which includes assessing whether the patient has premetastasized cervical cancer. This method comprises comparing the level of expression of a marker of the invention (listed in Table 1) in a patient sample and the normal level of expression of the marker in a control, *e.g.*, a non-cervical cancer sample. A significantly higher level of expression of the marker in the patient sample as compared to the normal level is an indication that the patient is afflicted with cervical cancer.

Gene delivery vehicles, host cells and compositions (all described herein) containing nucleic acids comprising the entirety, or a segment of 15 or more nucleotides, of any of the nucleic acid sequences set forth in the Sequence Listing, or the complement of such sequences, and polypeptides comprising the entirety, or a segment of 10 or more amino acids, of any of the amino acid sequences set forth in the Sequence Listing, are also provided by this invention.

As described herein, cervical cancer in patients is associated with an increased level of expression of one or more markers of the invention. While, as discussed above, some of these changes in expression level result from occurrence of the

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cervical cancer, others of these changes induce, maintain, and promote the cancerous state of cervical cancer cells. Thus, cervical cancer characterized by an increase in the level of expression of one or more markers of the invention can be inhibited by reducing and/or interfering with the expression of the markers and/or function of the proteins encoded by those markers.

Expression of a marker of the invention can be inhibited in a number of ways generally known in the art. For example, an antisense oligonucleotide can be provided to the cervical cancer cells in order to inhibit transcription, translation, or both, of the marker(s). Alternately, a polynucleotide encoding an antibody, an antibody derivative, or an antibody fragment which specifically binds a marker protein, and operably linked with an appropriate promoter/regulator region, can be provided to the cell in order to generate intracellular antibodies which will inhibit the function or activity of the protein. The expression and/or function of a marker may also be inhibited by treating the cervical cancer cell with an antibody, antibody derivative or antibody fragment that specifically binds a marker protein. Using the methods described herein, a variety of molecules, particularly including molecules sufficiently small that they are able to cross the cell membrane, can be screened in order to identify molecules which inhibit expression of a marker or inhibit the function of a marker protein. The compound so identified can be provided to the patient in order to inhibit cervical cancer cells of the patient.

Any marker or combination of markers of the invention, as well as any known markers in combination with the markers of the invention, may be used in the compositions, kits, and methods of the present invention. In general, it is preferable to use markers for which the difference between the level of expression of the marker in cervical cancer cells and the level of expression of the same marker in normal cervical cells is as great as possible. Although this difference can be as small as the limit of detection of the method for assessing expression of the marker, it is preferred that the difference be at least greater than the standard error of the assessment method, and preferably a difference of at least 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 15-, 20-, 25-, 100-, 500-, 1000-fold or greater than the level of expression of the same marker in normal cervical tissue.

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It is recognized that certain marker proteins are secreted from cervical cells (*i.e.* one or both of normal and cancerous cells) to the extracellular space surrounding the cells. These markers are preferably used in certain embodiments of the compositions, kits, and methods of the invention, owing to the fact that the such marker proteins can be detected in a cervical-associated body fluid sample, which may be more easily collected from a human patient than a tissue biopsy sample. In addition, preferred *in vivo* techniques for detection of a marker protein include introducing into a subject a labeled antibody directed against the protein. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

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It is a simple matter for the skilled artisan to determine whether any particular marker protein is a secreted protein. In order to make this determination, the marker protein is expressed in, for example, a mammalian cell, preferably a human cervical cell line, extracellular fluid is collected, and the presence or absence of the protein in the extracellular fluid is assessed (*e.g.* using a labeled antibody which binds specifically with the protein).

The following is an example of a method which can be used to detect secretion of a protein. About 8 x 10⁵ 293T cells are incubated at 37°C in wells containing growth medium (Dulbecco's modified Eagle's medium {DMEM} supplemented with 10% fetal bovine serum) under a 5% (v/v) CO₂, 95% air atmosphere to about 60-70% confluence. The cells are then transfected using a standard transfection mixture comprising 2 micrograms of DNA comprising an expression vector encoding the protein and 10 microliters of LipofectAMINETM (GIBCO/BRL Catalog no. 18342-012) per well. The transfection mixture is maintained for about 5 hours, and then replaced with fresh growth medium and maintained in an air atmosphere. Each well is gently rinsed twice with DMEM which does not contain methionine or cysteine (DMEM-MC; ICN Catalog no. 16-424-54). About 1 milliliter of DMEM-MC and about 50 microcuries of Trans-³⁵STM reagent (ICN Catalog no. 51006) are added to each well. The wells are maintained under the 5% CO₂ atmosphere described above and incubated at 37°C for a selected period. Following incubation, 150 microliters of conditioned medium is removed and centrifuged to remove floating cells and debris.

The presence of the protein in the supernatant is an indication that the protein is secreted.

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It will be appreciated that patient samples containing cervical cells may be used in the methods of the present invention. In these embodiments, the level of expression of the marker can be assessed by assessing the amount (e.g. absolute amount or concentration) of the marker in a cervical cell sample, e.g., cervical smear obtained from a patient. The cell sample can, of course, be subjected to a variety of well-known post-collection preparative and storage techniques (e.g., nucleic acid and/or protein extraction, fixation, storage, freezing, ultrafiltration, concentration, evaporation, centrifugation, etc.) prior to assessing the amount of the marker in the sample. Likewise, cervical smears may also be subjected to post-collection preparative and storage techniques, e.g., fixation.

The compositions, kits, and methods of the invention can be used to detect expression of marker proteins having at least one portion which is displayed on the surface of cells which express it. It is a simple matter for the skilled artisan to determine whether a marker protein, or a portion thereof, is exposed on the cell surface. For example, immunological methods may be used to detect such proteins on whole cells, or well known computer-based sequence analysis methods may be used to predict the presence of at least one extracellular domain (*i.e.* including both secreted proteins and proteins having at least one cell-surface domain). Expression of a marker protein having at least one portion which is displayed on the surface of a cell which expresses it may be detected without necessarily lysing the cell (*e.g.* using a labeled antibody which binds specifically with a cell-surface domain of the protein).

Expression of a marker of the invention may be assessed by any of a wide variety of well known methods for detecting expression of a transcribed nucleic acid or protein. Non-limiting examples of such methods include immunological methods for detection of secreted, cell-surface, cytoplasmic, or nuclear proteins, protein purification methods, protein function or activity assays, nucleic acid hybridization methods, nucleic acid reverse transcription methods, and nucleic acid amplification methods.

In a preferred embodiment, expression of a marker is assessed using an antibody (e.g. a radio-labeled, chromophore-labeled, fluorophore-labeled, or enzyme-labeled antibody), an antibody derivative (e.g. an antibody conjugated with a substrate or with the protein or ligand of a protein-ligand pair {e.g. biotin-streptavidin}), or an

antibody fragment (e.g. a single-chain antibody, an isolated antibody hypervariable domain, etc.) which binds specifically with a marker protein or fragment thereof, including a marker protein which has undergone all or a portion of its normal post-translational modification.

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In another preferred embodiment, expression of a marker is assessed by preparing mRNA/cDNA (*i.e.* a transcribed polynucleotide) from cells in a patient sample, and by hybridizing the mRNA/cDNA with a reference polynucleotide which is a complement of a marker nucleic acid, or a fragment thereof. cDNA can, optionally, be amplified using any of a variety of polymerase chain reaction methods prior to hybridization with the reference polynucleotide; preferably, it is not amplified. Expression of one or more markers can likewise be detected using quantitative PCR to assess the level of expression of the marker(s). Alternatively, any of the many known methods of detecting mutations or variants (*e.g.* single nucleotide polymorphisms, deletions, etc.) of a marker of the invention may be used to detect occurrence of a marker in a patient.

In a related embodiment, a mixture of transcribed polynucleotides obtained from the sample is contacted with a substrate having fixed thereto a polynucleotide complementary to or homologous with at least a portion (*e.g.* at least 7, 10, 15, 20, 25, 30, 40, 50, 100, 500, or more nucleotide residues) of a marker nucleic acid. If polynucleotides complementary to or homologous with are differentially detectable on the substrate (*e.g.* detectable using different chromophores or fluorophores, or fixed to different selected positions), then the levels of expression of a plurality of markers can be assessed simultaneously using a single substrate (*e.g.* a "gene chip" microarray of polynucleotides fixed at selected positions). When a method of assessing marker expression is used which involves hybridization of one nucleic acid with another, it is preferred that the hybridization be performed under stringent hybridization conditions.

Because the compositions, kits, and methods of the invention rely on detection of a difference in expression levels of one or more markers of the invention, it is preferable that the level of expression of the marker is significantly greater than the minimum detection limit of the method used to assess expression in at least one of normal cervical cells and cancerous cervical cells.

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It is understood that by routine screening of additional patient samples using one or more of the markers of the invention, it will be realized that certain of the markers are over-expressed in cancers of various types, including specific cervical cancers, as well as other cancers such as breast cancer, ovarian cancer, etc. For example, it will be confirmed that some of the markers of the invention are overexpressed in most (i.e. 50% or more) or substantially all (i.e. 80% or more) of cervical cancer. Furthermore, it will be confirmed that certain of the markers of the invention are associated with cervical cancer of various stages (i.e. stage 0, I, II, III, and IV cervical cancers, as well as subclassifications IA1, IA2, IB, IB1, IB2, IIA, IIB, IIIA, IIIB, IVA, and IVB, using the FIGO Stage Grouping system for primary carcinoma of the cervix (see Gynecologic Oncology, 1991, 41:199 and Cancer, 1992, 69:482)), and premalignant conditions (e.g., dysplasia including CIN or SIL), of various histologic subtypes (e.g. squamous cell carcinomas and squamous cell carcinoma variants such as verrucous carcinoma, lymphoepithelioma-like carcinoma, papillary squamous neoplasm and spindle cell squamous cell carcinoma (see Cervical Cancer and Preinvasive Neoplasia, 1996, pp. 90-91) serous, mucinous, endometrioid, and clear cell subtypes, as well as subclassifications and alternate classifications adenocarcinoma, papillary adenocarcinoma, papillary cystadenocarcinoma, surface papillary carcinoma, malignant adenofibroma, cystadenofibroma, adenocarcinoma, cystadenocarcinoma, adenoacanthoma, endometrioid stromal sarcoma, mesodermal {Müllerian} mixed tumor, malignant carcinoma, Brenner tumor, mixed epithelial tumor, and undifferentiated. carcinoma, using the WHO/FIGO system for classification of malignant cervical tumors; Scully, Atlas of Tumor Pathology, 3d series, Washington DC), and various grades (i.e. grade I {well differentiated}, grade II {moderately well differentiated}, and grade III {poorly differentiated from surrounding normal tissue}). In addition, as a greater number of patient samples are assessed for expression of the markers of the invention and the outcomes of the individual patients from whom the samples were obtained are correlated, it will also be confirmed that altered expression of certain of the markers of the invention are strongly correlated with malignant cancers and that altered expression of other markers of the invention are strongly correlated with benign tumors. The compositions, kits, and methods of the invention are thus useful for characterizing one or more of the stage, grade, histological type, and benign/malignant nature of cervical cancer in patients.

When the compositions, kits, and methods of the invention are used for characterizing one or more of the stage, grade, histological type, and benign/malignant nature of cervical cancer in a patient, it is preferred that the marker or panel of markers of the invention is selected such that a positive result is obtained in at least about 20%, and preferably at least about 40%, 60%, or 80%, and more preferably in substantially all patients afflicted with a cervical cancer of the corresponding stage, grade, histological type, or benign/malignant nature. Preferably, the marker or panel of markers of the invention is selected such that a positive predictive value (PPV) of greater than about 10% is obtained for the general population (more preferably coupled with an assay specificity greater than 80%).

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When a plurality of markers of the invention are used in the compositions, kits, and methods of the invention, the level of expression of each marker in a patient sample can be compared with the normal level of expression of each of the plurality of markers in non-cancerous samples of the same type, either in a single reaction mixture (*i.e.* using reagents, such as different fluorescent probes, for each marker) or in individual reaction mixtures corresponding to one or more of the markers. In one embodiment, a significantly increased level of expression of more than one of the plurality of markers in the sample, relative to the corresponding normal levels, is an indication that the patient is afflicted with cervical cancer. When a plurality of markers is used, it is preferred that 2, 3, 4, 5, 8, 10, 12, 15, 20, 30, or 50 or more individual markers be used, wherein fewer markers are preferred.

In order to maximize the sensitivity of the compositions, kits, and methods of the invention (*i.e.* by interference attributable to cells of non-cervical origin in a patient sample), it is preferable that the marker of the invention used therein be a marker which has a restricted tissue distribution, *e.g.*, normally not expressed in a non-cervical tissue.

Only a small number of markers are known to be associated with cervical cancer (e.g. bcl-2, 15A8 antigen, cdc6, Mcm5, and EGFR). These markers are not, of course, included among the markers of the invention, although they may be used together with one or more markers of the invention in a panel of markers, for example. It is well known that certain types of genes, such as oncogenes, tumor suppressor genes, growth factor-like genes, protease-like genes, and protein kinase-like genes are often involved with development of cancers of various types. Thus, among the markers of the

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invention, use of those which correspond to proteins which resemble known proteins encoded by known oncogenes and tumor suppressor genes, and those which correspond to proteins which resemble growth factors, proteases, and protein kinases are preferred.

It is recognized that the compositions, kits, and methods of the invention will be of particular utility to patients having an enhanced risk of developing cervical cancer and their medical advisors. Patients recognized as having an enhanced risk of developing cervical cancer include, for example, patients having a familial history of cervical cancer, patients identified as having a mutant oncogene (*i.e.* at least one allele), and patients of advancing age (*i.e.* women older than about 50 or 60 years).

The level of expression of a marker in normal (*i.e.* non-cancerous) human cervical tissue can be assessed in a variety of ways. In one embodiment, this normal level of expression is assessed by assessing the level of expression of the marker in a portion of cervical cells which appears to be non-cancerous and by comparing this normal level of expression with the level of expression in a portion of the cervical cells which is suspected of being cancerous. Alternately, and particularly as further information becomes available as a result of routine performance of the methods described herein, population-average values for normal expression of the markers of the invention may be used. In other embodiments, the 'normal' level of expression of a marker may be determined by assessing expression of the marker in a patient sample obtained from a non-cancer-afflicted patient, from a patient sample obtained from a patient before the suspected onset of cervical cancer in the patient, from archived patient samples, and the like.

The invention includes compositions, kits, and methods for assessing the presence of cervical cancer cells in a sample (e.g. an archived tissue sample or a sample obtained from a patient). These compositions, kits, and methods are substantially the same as those described above, except that, where necessary, the compositions, kits, and methods are adapted for use with samples other than patient samples. For example, when the sample to be used is a parafinized, archived human tissue sample, it can be necessary to adjust the ratio of compounds in the compositions of the invention, in the kits of the invention, or the methods used to assess levels of marker expression in the sample. Such methods are well known in the art and within the skill of the ordinary artisan.

The invention includes a kit for assessing the presence of cervical cancer cells (*e.g.* in a sample such as a patient sample). The kit comprises a plurality of reagents, each of which is capable of binding specifically with a marker nucleic acid or protein. Suitable reagents for binding with a marker protein include antibodies, antibody derivatives, antibody fragments, and the like. Suitable reagents for binding with a marker nucleic acid (*e.g.* a genomic DNA, an mRNA, a spliced mRNA, a cDNA, or the like) include complementary nucleic acids. For example, the nucleic acid reagents may include oligonucleotides (labeled or non-labeled) fixed to a substrate, labeled oligonucleotides not bound with a substrate, pairs of PCR primers, molecular beacon probes, and the like.

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The kit of the invention may optionally comprise additional components useful for performing the methods of the invention. By way of example, the kit may comprise fluids (e.g. SSC buffer) suitable for annealing complementary nucleic acids or for binding an antibody with a protein with which it specifically binds, one or more sample compartments, an instructional material which describes performance of a method of the invention, a sample of normal cervical cells, a sample of cervical cancer cells, and the like.

The invention also includes a method of making an isolated hybridoma which produces an antibody useful for assessing whether patient is afflicted with an cervical cancer. In this method, a protein or peptide comprising the entirety or a segment of a marker protein is synthesized or isolated (e.g. by purification from a cell in which it is expressed or by transcription and translation of a nucleic acid encoding the protein or peptide in vivo or in vitro using known methods). A vertebrate, preferably a mammal such as a mouse, rat, rabbit, or sheep, is immunized using the protein or peptide. The vertebrate may optionally (and preferably) be immunized at least one additional time with the protein or peptide, so that the vertebrate exhibits a robust immune response to the protein or peptide. Splenocytes are isolated from the immunized vertebrate and fused with an immortalized cell line to form hybridomas, using any of a variety of methods well known in the art. Hybridomas formed in this manner are then screened using standard methods to identify one or more hybridomas which produce an antibody which specifically binds with the marker protein or a fragment thereof. The invention also includes hybridomas made by this method and antibodies made using such hybridomas.

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The invention also includes a method of assessing the efficacy of a test compound for inhibiting cervical cancer cells. As described above, differences in the level of expression of the markers of the invention correlate with the cancerous state of cervical cells. Although it is recognized that changes in the levels of expression of certain of the markers of the invention likely result from the cancerous state of cervical cells, it is likewise recognized that changes in the levels of expression of other of the markers of the invention induce, maintain, and promote the cancerous state of those cells. Thus, compounds which inhibit an cervical cancer in a patient will cause the level of expression of one or more of the markers of the invention to change to a level nearer the normal level of expression for that marker (*i.e.* the level of expression for the marker in non-cancerous cervical cells).

This method thus comprises comparing expression of a marker in a first cervical cell sample and maintained in the presence of the test compound and expression of the marker in a second cervical cell sample and maintained in the absence of the test compound. A significantly reduced expression of a marker of the invention in the presence of the test compound is an indication that the test compound inhibits cervical cancer. The cervical cell samples may, for example, be aliquots of a single sample of normal cervical cells obtained from a patient, pooled samples of normal cervical cells obtained from a patient, cells of a normal cervical cell line, aliquots of a single sample of cervical cancer cells obtained from a patient, pooled samples of cervical cancer cells obtained from a patient, cells of an cervical cancer cell line, or the like. In one embodiment, the samples are cervical cancer cells obtained from a patient and a plurality of compounds known to be effective for inhibiting various cervical cancers are tested in order to identify the compound which is likely to best inhibit the cervical cancer in the patient.

This method may likewise be used to assess the efficacy of a therapy for inhibiting cervical cancer in a patient. In this method, the level of expression of one or more markers of the invention in a pair of samples (one subjected to the therapy, the other not subjected to the therapy) is assessed. As with the method of assessing the efficacy of test compounds, if the therapy induces a significantly lower level of expression of a marker of the invention then the therapy is efficacious for inhibiting cervical cancer. As above, if samples from a selected patient are used in this method,

then alternative therapies can be assessed *in vitro* in order to select a therapy most likely to be efficacious for inhibiting cervical cancer in the patient.

As described above, the cancerous state of human cervical cells is correlated with changes in the levels of expression of the markers of the invention. The invention includes a method for assessing the human cervical cell carcinogenic potential of a test compound. This method comprises maintaining separate aliquots of human cervical cells in the presence and absence of the test compound. Expression of a marker of the invention in each of the aliquots is compared. A significantly higher level of expression of a marker of the invention in the aliquot maintained in the presence of the test compound (relative to the aliquot maintained in the absence of the test compound) is an indication that the test compound possesses human cervical cell carcinogenic potential. The relative carcinogenic potentials of various test compounds can be assessed by comparing the degree of enhancement or inhibition of the level of expression of the relevant markers, by comparing the number of markers for which the level of expression is enhanced or inhibited, or by comparing both.

Various aspects of the invention are described in further detail in the following subsections.

I. Isolated Nucleic Acid Molecules

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One aspect of the invention pertains to isolated nucleic acid molecules, including nucleic acids which encode a marker protein or a portion thereof. Isolated nucleic acids of the invention also include nucleic acid molecules sufficient for use as hybridization probes to identify marker nucleic acid molecules, and fragments of marker nucleic acid molecules, *e.g.*, those suitable for use as PCR primers for the amplification or mutation of marker nucleic acid molecules. As used herein, the term "nucleic acid molecule" is intended to include DNA molecules (*e.g.*, cDNA or genomic DNA) and RNA molecules (*e.g.*, mRNA) and analogs of the DNA or RNA generated using nucleotide analogs. The nucleic acid molecule can be single-stranded or double-stranded, but preferably is double-stranded DNA.

An "isolated" nucleic acid molecule is one which is separated from other nucleic acid molecules which are present in the natural source of the nucleic acid molecule. Preferably, an "isolated" nucleic acid molecule is free of sequences (preferably protein-encoding sequences) which naturally flank the nucleic acid (i.e.,

sequences located at the 5' and 3' ends of the nucleic acid) in the genomic DNA of the organism from which the nucleic acid is derived. For example, in various embodiments, the isolated nucleic acid molecule can contain less than about 5 kB, 4 kB, 3 kB, 2 kB, 1 kB, 0.5 kB or 0.1 kB of nucleotide sequences which naturally flank the nucleic acid molecule in genomic DNA of the cell from which the nucleic acid is derived. Moreover, an "isolated" nucleic acid molecule, such as a cDNA molecule, can be substantially free of other cellular material, or culture medium when produced by recombinant techniques, or substantially free of chemical precursors or other chemicals when chemically synthesized.

A nucleic acid molecule of the present invention can be isolated using standard molecular biology techniques and the sequence information in the database records described herein. Using all or a portion of such nucleic acid sequences, nucleic acid molecules of the invention can be isolated using standard hybridization and cloning techniques (e.g., as described in Sambrook et al., ed., Molecular Cloning: A Laboratory Manual, 2nd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989).

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A nucleic acid molecule of the invention can be amplified using cDNA, mRNA, or genomic DNA as a template and appropriate oligonucleotide primers according to standard PCR amplification techniques. The nucleic acid so amplified can be cloned into an appropriate vector and characterized by DNA sequence analysis. Furthermore, nucleotides corresponding to all or a portion of a nucleic acid molecule of the invention can be prepared by standard synthetic techniques, *e.g.*, using an automated DNA synthesizer.

In another preferred embodiment, an isolated nucleic acid molecule of the invention comprises a nucleic acid molecule which has a nucleotide sequence complementary to the nucleotide sequence of a marker nucleic acid or to the nucleotide sequence of a nucleic acid encoding a marker protein. A nucleic acid molecule which is complementary to a given nucleotide sequence is one which is sufficiently complementary to the given nucleotide sequence that it can hybridize to the given nucleotide sequence thereby forming a stable duplex.

Moreover, a nucleic acid molecule of the invention can comprise only a portion of a nucleic acid sequence, wherein the full length nucleic acid sequence comprises a marker nucleic acid or which encodes a marker protein. Such nucleic acids

can be used, for example, as a probe or primer. The probe/primer typically is used as one or more substantially purified oligonucleotides. The oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 7, preferably about 15, more preferably about 25, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, or 400 or more consecutive nucleotides of a nucleic acid of the invention.

Probes based on the sequence of a nucleic acid molecule of the invention can be used to detect transcripts or genomic sequences corresponding to one or more markers of the invention. The probe comprises a label group attached thereto, *e.g.*, a radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor. Such probes can be used as part of a diagnostic test kit for identifying cells or tissues which misexpress the protein, such as by measuring levels of a nucleic acid molecule encoding the protein in a sample of cells from a subject, *e.g.*, detecting mRNA levels or determining whether a gene encoding the protein has been mutated or deleted.

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The invention further encompasses nucleic acid molecules that differ, due to degeneracy of the genetic code, from the nucleotide sequence of nucleic acids encoding a marker protein (e.g., a protein having one of the amino acid sequences set forth in the Sequence Listing), and thus encode the same protein.

It will be appreciated by those skilled in the art that DNA sequence polymorphisms that lead to changes in the amino acid sequence can exist within a population (e.g., the human population). Such genetic polymorphisms can exist among individuals within a population due to natural allelic variation. An allele is one of a group of genes which occur alternatively at a given genetic locus. In addition, it will be appreciated that DNA polymorphisms that affect RNA expression levels can also exist that may affect the overall expression level of that gene (e.g., by affecting regulation or degradation).

As used herein, the phrase "allelic variant" refers to a nucleotide sequence which occurs at a given locus or to a polypeptide encoded by the nucleotide sequence.

As used herein, the terms "gene" and "recombinant gene" refer to nucleic acid molecules comprising an open reading frame encoding a polypeptide corresponding to a marker of the invention. Such natural allelic variations can typically result in 1-5% variance in the nucleotide sequence of a given gene. Alternative alleles can be identified by sequencing the gene of interest in a number of different individuals. This can be

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readily carried out by using hybridization probes to identify the same genetic locus in a variety of individuals. Any and all such nucleotide variations and resulting amino acid polymorphisms or variations that are the result of natural allelic variation and that do not alter the functional activity are intended to be within the scope of the invention.

In another embodiment, an isolated nucleic acid molecule of the invention is at least 7, 15, 20, 25, 30, 40, 60, 80, 100, 150, 200, 250, 300, 350, 400, 450, 550, 650, 700, 800, 900, 1000, 1200, 1400, 1600, 1800, 2000, 2200, 2400, 2600, 2800, 3000, 3500, 4000, 4500, or more nucleotides in length and hybridizes under stringent conditions to a marker nucleic acid or to a nucleic acid encoding a marker protein. As used herein, the term "hybridizes under stringent conditions" is intended to describe conditions for hybridization and washing under which nucleotide sequences at least 60% (65%, 70%, preferably 75%) identical to each other typically remain hybridized to each other. Such stringent conditions are known to those skilled in the art and can be found in sections 6.3.1-6.3.6 of *Current Protocols in Molecular Biology*, John Wiley & Sons, N.Y. (1989). A preferred, non-limiting example of stringent hybridization conditions are hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 50-65°C.

In addition to naturally-occurring allelic variants of a nucleic acid molecule of the invention that can exist in the population, the skilled artisan will further appreciate that sequence changes can be introduced by mutation thereby leading to changes in the amino acid sequence of the encoded protein, without altering the biological activity of the protein encoded thereby. For example, one can make nucleotide substitutions leading to amino acid substitutions at "non-essential" amino acid residues. A "non-essential" amino acid residue is a residue that can be altered from the wild-type sequence without altering the biological activity, whereas an "essential" amino acid residue is required for biological activity. For example, amino acid residues that are not conserved or only semi-conserved among homologs of various species may be non-essential for activity and thus would be likely targets for alteration.

Alternatively, amino acid residues that are conserved among the homologs of various species (e.g., murine and human) may be essential for activity and thus would not be likely targets for alteration.

Accordingly, another aspect of the invention pertains to nucleic acid molecules encoding a variant marker protein that contain changes in amino acid residues that are not essential for activity. Such variant marker proteins differ in amino acid sequence from the naturally-occurring marker proteins, yet retain biological activity. In one embodiment, such a variant marker protein has an amino acid sequence that is at least about 40% identical, 50%, 60%, 70%, 80%, 90%, 95%, or 98% identical to the amino acid sequence of a marker protein.

An isolated nucleic acid molecule encoding a variant marker protein can be created by introducing one or more nucleotide substitutions, additions or deletions into the nucleotide sequence of marker nucleic acids, such that one or more amino acid residue substitutions, additions, or deletions are introduced into the encoded protein. Mutations can be introduced by standard techniques, such as site-directed mutagenesis and PCR-mediated mutagenesis. Preferably, conservative amino acid substitutions are made at one or more predicted non-essential amino acid residues. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), non-polar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine). Alternatively, mutations can be introduced randomly along all or part of the coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for biological activity to identify mutants that retain activity. Following mutagenesis, the encoded protein can be expressed recombinantly and the activity of the protein can be determined.

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The present invention encompasses antisense nucleic acid molecules, *i.e.*, molecules which are complementary to a sense nucleic acid of the invention, *e.g.*, complementary to the coding strand of a double-stranded marker cDNA molecule or complementary to a marker mRNA sequence. Accordingly, an antisense nucleic acid of the invention can hydrogen bond to (*i.e.* anneal with) a sense nucleic acid of the invention. The antisense nucleic acid can be complementary to an entire coding strand,

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or to only a portion thereof, *e.g.*, all or part of the protein coding region (or open reading frame). An antisense nucleic acid molecule can also be antisense to all or part of a non-coding region of the coding strand of a nucleotide sequence encoding a marker protein. The non-coding regions ("5' and 3' untranslated regions") are the 5' and 3' sequences which flank the coding region and are not translated into amino acids.

An antisense oligonucleotide can be, for example, about 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 or more nucleotides in length. An antisense nucleic acid of the invention can be constructed using chemical synthesis and enzymatic ligation reactions using procedures known in the art. For example, an antisense nucleic acid (e.g., an antisense oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids, e.g., phosphorothioate derivatives and acridine substituted nucleotides can be used. Examples of modified nucleotides which can be used to generate the antisense nucleic acid include 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxylmethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine. Alternatively, the antisense nucleic acid can be produced biologically using an expression vector into which a nucleic acid has been sub-cloned in an antisense orientation (i.e., RNA transcribed from the inserted nucleic acid will be of an antisense orientation to a target nucleic acid of interest, described further in the following subsection).

The antisense nucleic acid molecules of the invention are typically administered to a subject or generated in situ such that they hybridize with or bind to cellular mRNA and/or genomic DNA encoding a marker protein to thereby inhibit expression of the marker, e.g., by inhibiting transcription and/or translation. The hybridization can be by conventional nucleotide complementarity to form a stable duplex, or, for example, in the case of an antisense nucleic acid molecule which binds to DNA duplexes, through specific interactions in the major groove of the double helix. Examples of a route of administration of antisense nucleic acid molecules of the invention includes direct injection at a tissue site or infusion of the antisense nucleic acid into an ovary-associated body fluid. Alternatively, antisense nucleic acid molecules can be modified to target selected cells and then administered systemically. For example, for systemic administration, antisense molecules can be modified such that they specifically bind to receptors or antigens expressed on a selected cell surface, e.g., by linking the antisense nucleic acid molecules to peptides or antibodies which bind to cell surface receptors or antigens. The antisense nucleic acid molecules can also be delivered to cells using the vectors described herein. To achieve sufficient intracellular concentrations of the antisense molecules, vector constructs in which the antisense nucleic acid molecule is placed under the control of a strong pol II or pol III promoter are preferred.

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An antisense nucleic acid molecule of the invention can be an α-anomeric nucleic acid molecule. An α-anomeric nucleic acid molecule forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual α-units, the strands run parallel to each other (Gaultier *et al.*, 1987, *Nucleic Acids Res.* 15:6625-6641). The antisense nucleic acid molecule can also comprise a 2'-o-methylribonucleotide (Inoue *et al.*, 1987, *Nucleic Acids Res.* 15:6131-6148) or a chimeric RNA-DNA analogue (Inoue *et al.*, 1987, *FEBS Lett.* 215:327-330).

The invention also encompasses ribozymes. Ribozymes are catalytic RNA molecules with ribonuclease activity which are capable of cleaving a single-stranded nucleic acid, such as an mRNA, to which they have a complementary region. Thus, ribozymes (e.g., hammerhead ribozymes as described in Haselhoff and Gerlach, 1988, *Nature* 334:585-591) can be used to catalytically cleave mRNA transcripts to thereby inhibit translation of the protein encoded by the mRNA. A ribozyme having specificity for a nucleic acid molecule encoding a marker protein can be designed based

upon the nucleotide sequence of a cDNA corresponding to the marker. For example, a derivative of a *Tetrahymena* L-19 IVS RNA can be constructed in which the nucleotide sequence of the active site is complementary to the nucleotide sequence to be cleaved (see Cech *et al.* U.S. Patent No. 4,987,071; and Cech *et al.* U.S. Patent No. 5,116,742).

Alternatively, an mRNA encoding a polypeptide of the invention can be used to select a catalytic RNA having a specific ribonuclease activity from a pool of RNA molecules (see, e.g., Bartel and Szostak, 1993, *Science* 261:1411-1418).

The invention also encompasses nucleic acid molecules which form triple helical structures. For example, expression of a marker of the invention can be inhibited by targeting nucleotide sequences complementary to the regulatory region of the gene encoding the marker nucleic acid or protein (e.g., the promoter and/or enhancer) to form triple helical structures that prevent transcription of the gene in target cells. See generally Helene (1991) Anticancer Drug Des. 6(6):569-84; Helene (1992) Ann. N.Y. Acad. Sci. 660:27-36; and Maher (1992) Bioassays 14(12):807-15.

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In various embodiments, the nucleic acid molecules of the invention can be modified at the base moiety, sugar moiety or phosphate backbone to improve, e.g., the stability, hybridization, or solubility of the molecule. For example, the deoxyribose phosphate backbone of the nucleic acids can be modified to generate peptide nucleic acids (see Hyrup et al., 1996, Bioorganic & Medicinal Chemistry 4(1): 5-23). As used herein, the terms "peptide nucleic acids" or "PNAs" refer to nucleic acid mimics, e.g., DNA mimics, in which the deoxyribose phosphate backbone is replaced by a pseudopeptide backbone and only the four natural nucleobases are retained. The neutral backbone of PNAs has been shown to allow for specific hybridization to DNA and RNA under conditions of low ionic strength. The synthesis of PNA oligomers can be performed using standard solid phase peptide synthesis protocols as described in Hyrup et al. (1996), supra; Perry-O'Keefe et al. (1996) Proc. Natl. Acad. Sci. USA 93:14670-675.

PNAs can be used in therapeutic and diagnostic applications. For example, PNAs can be used as antisense or antigene agents for sequence-specific modulation of gene expression by, *e.g.*, inducing transcription or translation arrest or inhibiting replication. PNAs can also be used, *e.g.*, in the analysis of single base pair mutations in a gene by, *e.g.*, PNA directed PCR clamping; as artificial restriction enzymes when used in combination with other enzymes, *e.g.*, S1 nucleases (Hyrup

(1996), *supra*; or as probes or primers for DNA sequence and hybridization (Hyrup, 1996, *supra*; Perry-O'Keefe *et al.*, 1996, *Proc. Natl. Acad. Sci. USA* 93:14670-675).

In another embodiment, PNAs can be modified, e.g., to enhance their stability or cellular uptake, by attaching lipophilic or other helper groups to PNA, by the formation of PNA-DNA chimeras, or by the use of liposomes or other techniques of drug delivery known in the art. For example, PNA-DNA chimeras can be generated which can combine the advantageous properties of PNA and DNA. Such chimeras allow DNA recognition enzymes, e.g., RNase H and DNA polymerases, to interact with the DNA portion while the PNA portion would provide high binding affinity and specificity. PNA-DNA chimeras can be linked using linkers of appropriate lengths selected in terms of base stacking, number of bonds between the nucleobases, and orientation (Hyrup, 1996, supra). The synthesis of PNA-DNA chimeras can be performed as described in Hyrup (1996), supra, and Finn et al. (1996) Nucleic Acids Res. 24(17):3357-63. For example, a DNA chain can be synthesized on a solid support using standard phosphoramidite coupling chemistry and modified nucleoside analogs. Compounds such as 5'-(4-methoxytrityl)amino-5'-deoxy-thymidine phosphoramidite can be used as a link between the PNA and the 5' end of DNA (Mag et al., 1989, Nucleic Acids Res. 17:5973-88). PNA monomers are then coupled in a step-wise manner to produce a chimeric molecule with a 5' PNA segment and a 3' DNA segment (Finn et al., 1996, Nucleic Acids Res. 24(17):3357-63). Alternatively, chimeric molecules can be synthesized with a 5' DNA segment and a 3' PNA segment (Peterser et al., 1975, Bioorganic Med. Chem. Lett. 5:1119-11124).

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In other embodiments, the oligonucleotide can include other appended groups such as peptides (*e.g.*, for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell membrane (see, *e.g.*, Letsinger *et al.*, 1989, *Proc. Natl. Acad. Sci. USA* 86:6553-6556; Lemaitre *et al.*, 1987, *Proc. Natl. Acad. Sci. USA* 84:648-652; PCT Publication No. WO 88/09810) or the blood-brain barrier (see, *e.g.*, PCT Publication No. WO 89/10134). In addition, oligonucleotides can be modified with hybridization-triggered cleavage agents (see, *e.g.*, Krol *et al.*, 1988, *Bio/Techniques* 6:958-976) or intercalating agents (see, *e.g.*, Zon, 1988, *Pharm. Res.* 5:539-549). To this end, the oligonucleotide can be conjugated to another molecule, *e.g.*, a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

The invention also includes molecular beacon nucleic acids having at least one region which is complementary to a nucleic acid of the invention, such that the molecular beacon is useful for quantitating the presence of the nucleic acid of the invention in a sample. A "molecular beacon" nucleic acid is a nucleic acid comprising a pair of complementary regions and having a fluorophore and a fluorescent quencher associated therewith. The fluorophore and quencher are associated with different portions of the nucleic acid in such an orientation that when the complementary regions are annealed with one another, fluorescence of the fluorophore is quenched by the quencher. When the complementary regions of the nucleic acid are not annealed with one another, fluorescence of the fluorophore is quenched to a lesser degree. Molecular beacon nucleic acids are described, for example, in U.S. Patent 5,876,930.

II. Isolated Proteins and Antibodies

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One aspect of the invention pertains to isolated marker proteins and biologically active portions thereof, as well as polypeptide fragments suitable for use as immunogens to raise antibodies directed against a marker protein or a fragment thereof. In one embodiment, the native marker protein can be isolated from cells or tissue sources by an appropriate purification scheme using standard protein purification techniques. In another embodiment, a protein or peptide comprising the whole or a segment of the marker protein is produced by recombinant DNA techniques. Alternative to recombinant expression, such protein or peptide can be synthesized chemically using standard peptide synthesis techniques.

An "isolated" or "purified" protein or biologically active portion thereof is substantially free of cellular material or other contaminating proteins from the cell or tissue source from which the protein is derived, or substantially free of chemical precursors or other chemicals when chemically synthesized. The language "substantially free of cellular material" includes preparations of protein in which the protein is separated from cellular components of the cells from which it is isolated or recombinantly produced. Thus, protein that is substantially free of cellular material includes preparations of protein having less than about 30%, 20%, 10%, or 5% (by dry weight) of heterologous protein (also referred to herein as a "contaminating protein"). When the protein or biologically active portion thereof is recombinantly produced, it is also preferably substantially free of culture medium, *i.e.*, culture medium represents less

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than about 20%, 10%, or 5% of the volume of the protein preparation. When the protein is produced by chemical synthesis, it is preferably substantially free of chemical precursors or other chemicals, *i.e.*, it is separated from chemical precursors or other chemicals which are involved in the synthesis of the protein. Accordingly such preparations of the protein have less than about 30%, 20%, 10%, 5% (by dry weight) of chemical precursors or compounds other than the polypeptide of interest.

Biologically active portions of a marker protein include polypeptides comprising amino acid sequences sufficiently identical to or derived from the amino acid sequence of the marker protein, which include fewer amino acids than the full length protein, and exhibit at least one activity of the corresponding full-length protein. Typically, biologically active portions comprise a domain or motif with at least one activity of the corresponding full-length protein. A biologically active portion of a marker protein of the invention can be a polypeptide which is, for example, 10, 25, 50, 100 or more amino acids in length. Moreover, other biologically active portions, in which other regions of the marker protein are deleted, can be prepared by recombinant techniques and evaluated for one or more of the functional activities of the native form of the marker protein.

Preferred marker proteins are encoded by nucleotide sequences comprising the sequence of any of the sequences set forth in the Sequence Listing. Other useful proteins are substantially identical (e.g., at least about 40%, preferably 50%, 60%, 70%, 80%, 90%, 95%, or 99%) to one of these sequences and retain the functional activity of the corresponding naturally-occurring marker protein yet differ in amino acid sequence due to natural allelic variation or mutagenesis.

To determine the percent identity of two amino acid sequences or of two nucleic acids, the sequences are aligned for optimal comparison purposes (e.g., gaps can be introduced in the sequence of a first amino acid or nucleic acid sequence for optimal alignment with a second amino or nucleic acid sequence). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (i.e., %

identity = # of identical positions/total # of positions (e.g., overlapping positions) x100). In one embodiment the two sequences are the same length.

The determination of percent identity between two sequences can be accomplished using a mathematical algorithm. A preferred, non-limiting example of a mathematical algorithm utilized for the comparison of two sequences is the algorithm of Karlin and Altschul (1990) Proc. Natl. Acad. Sci. USA 87:2264-2268, modified as in Karlin and Altschul (1993) Proc. Natl. Acad. Sci. USA 90:5873-5877. Such an algorithm is incorporated into the BLASTN and BLASTX programs of Altschul, et al. (1990) J. Mol. Biol. 215:403-410. BLAST nucleotide searches can be performed with the BLASTN program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to a nucleic acid molecules of the invention. BLAST protein searches can be performed with the BLASTP program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to a protein molecules of the invention. To obtain gapped alignments for comparison purposes, a newer version of the BLAST algorithm called Gapped BLAST can be utilized as described in Altschul et al. (1997) Nucleic Acids Res. 25:3389-3402, which is able to perform gapped local alignments for the programs BLASTN, BLASTP and BLASTX. Alternatively, PSI-Blast can be used to perform an iterated search which detects distant relationships between molecules. When utilizing BLAST, Gapped BLAST, and PSI-Blast programs, the default parameters of the respective programs (e.g., BLASTX and BLASTN) can be used. See http://www.ncbi.nlm.nih.gov. Another preferred, non-limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, (1988) CABIOS 4:11-17. Such an algorithm is incorporated into the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used. Yet another useful algorithm for identifying regions of local sequence similarity and alignment is the FASTA algorithm as described in Pearson and Lipman (1988) Proc. Natl. Acad. Sci. USA 85:2444-2448. When using the FASTA algorithm for comparing nucleotide or amino acid sequences, a PAM120 weight residue table can, for example, be used with a k-tuple value of 2.

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The percent identity between two sequences can be determined using techniques similar to those described above, with or without allowing gaps. In calculating percent identity, only exact matches are counted.

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The invention also provides chimeric or fusion proteins comprising a marker protein or a segment thereof. As used herein, a "chimeric protein" or "fusion protein" comprises all or part (preferably a biologically active part) of a marker protein operably linked to a heterologous polypeptide (*i.e.*, a polypeptide other than the marker protein). Within the fusion protein, the term "operably linked" is intended to indicate that the marker protein or segment thereof and the heterologous polypeptide are fused in-frame to each other. The heterologous polypeptide can be fused to the aminoterminus or the carboxyl-terminus of the marker protein or segment.

One useful fusion protein is a GST fusion protein in which a marker protein or segment is fused to the carboxyl terminus of GST sequences. Such fusion proteins can facilitate the purification of a recombinant polypeptide of the invention.

In another embodiment, the fusion protein contains a heterologous signal sequence at its amino terminus. For example, the native signal sequence of a marker protein can be removed and replaced with a signal sequence from another protein. For example, the gp67 secretory sequence of the baculovirus envelope protein can be used as a heterologous signal sequence (Ausubel *et al.*, ed., *Current Protocols in Molecular Biology*, John Wiley & Sons, NY, 1992). Other examples of eukaryotic heterologous signal sequences include the secretory sequences of melittin and human placental alkaline phosphatase (Stratagene; La Jolla, California). In yet another example, useful prokaryotic heterologous signal sequences include the phoA secretory signal (Sambrook *et al.*, *supra*) and the protein A secretory signal (Pharmacia Biotech; Piscataway, New Jersey).

In yet another embodiment, the fusion protein is an immunoglobulin fusion protein in which all or part of a marker protein is fused to sequences derived from a member of the immunoglobulin protein family. The immunoglobulin fusion proteins of the invention can be incorporated into pharmaceutical compositions and administered to a subject to inhibit an interaction between a ligand (soluble or membrane-bound) and a protein on the surface of a cell (receptor), to thereby suppress signal transduction *in vivo*. The immunoglobulin fusion protein can be used to affect the bioavailability of a cognate ligand of a marker protein. Inhibition of ligand/receptor interaction can be

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useful therapeutically, both for treating proliferative and differentiative disorders and for modulating (e.g. promoting or inhibiting) cell survival. Moreover, the immunoglobulin fusion proteins of the invention can be used as immunogens to produce antibodies directed against a marker protein in a subject, to purify ligands and in screening assays to identify molecules which inhibit the interaction of the marker protein with ligands.

Chimeric and fusion proteins of the invention can be produced by standard recombinant DNA techniques. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of gene fragments can be carried out using anchor primers which give rise to complementary overhangs between two consecutive gene fragments which can subsequently be annealed and re-amplified to generate a chimeric gene sequence (see, e.g., Ausubel et al., supra). Moreover, many expression vectors are commercially available that already encode a fusion moiety (e.g., a GST polypeptide). A nucleic acid encoding a polypeptide of the invention can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the polypeptide of the invention.

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A signal sequence can be used to facilitate secretion and isolation of marker proteins. Signal sequences are typically characterized by a core of hydrophobic amino acids which are generally cleaved from the mature protein during secretion in one or more cleavage events. Such signal peptides contain processing sites that allow cleavage of the signal sequence from the mature proteins as they pass through the secretory pathway. Thus, the invention pertains to marker proteins, fusion proteins or segments thereof having a signal sequence, as well as to such proteins from which the signal sequence has been proteolytically cleaved (i.e., the cleavage products). In one embodiment, a nucleic acid sequence encoding a signal sequence can be operably linked in an expression vector to a protein of interest, such as a marker protein or a segment thereof. The signal sequence directs secretion of the protein, such as from a eukaryotic host into which the expression vector is transformed, and the signal sequence is subsequently or concurrently cleaved. The protein can then be readily purified from the extracellular medium by art recognized methods. Alternatively, the signal sequence can be linked to the protein of interest using a sequence which facilitates purification, such as with a GST domain.

The present invention also pertains to variants of the marker proteins. Such variants have an altered amino acid sequence which can function as either agonists (mimetics) or as antagonists. Variants can be generated by mutagenesis, *e.g.*, discrete point mutation or truncation. An agonist can retain substantially the same, or a subset, of the biological activities of the naturally occurring form of the protein. An antagonist of a protein can inhibit one or more of the activities of the naturally occurring form of the protein by, for example, competitively binding to a downstream or upstream member of a cellular signaling cascade which includes the protein of interest. Thus, specific biological effects can be elicited by treatment with a variant of limited function.

Treatment of a subject with a variant having a subset of the biological activities of the naturally occurring form of the protein can have fewer side effects in a subject relative to treatment with the naturally occurring form of the protein.

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Variants of a marker protein which function as either agonists (mimetics) or as antagonists can be identified by screening combinatorial libraries of mutants, *e.g.*, truncation mutants, of the protein of the invention for agonist or antagonist activity. In one embodiment, a variegated library of variants is generated by combinatorial mutagenesis at the nucleic acid level and is encoded by a variegated gene library. A variegated library of variants can be produced by, for example, enzymatically ligating a mixture of synthetic oligonucleotides into gene sequences such that a degenerate set of potential protein sequences is expressible as individual polypeptides, or alternatively, as a set of larger fusion proteins (*e.g.*, for phage display). There are a variety of methods which can be used to produce libraries of potential variants of the marker proteins from a degenerate oligonucleotide sequence. Methods for synthesizing degenerate oligonucleotides are known in the art (see, *e.g.*, Narang, 1983, *Tetrahedron* 39:3; Itakura *et al.*, 1984, *Annu. Rev. Biochem.* 53:323; Itakura *et al.*, 1984, *Science* 198:1056; Ike *et al.*, 1983 *Nucleic Acid Res.* 11:477).

In addition, libraries of segments of a marker protein can be used to generate a variegated population of polypeptides for screening and subsequent selection of variant marker proteins or segments thereof. For example, a library of coding sequence fragments can be generated by treating a double stranded PCR fragment of the coding sequence of interest with a nuclease under conditions wherein nicking occurs only about once per molecule, denaturing the double stranded DNA, renaturing the DNA to form double stranded DNA which can include sense/antisense pairs from different

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nicked products, removing single stranded portions from reformed duplexes by treatment with S1 nuclease, and ligating the resulting fragment library into an expression vector. By this method, an expression library can be derived which encodes amino terminal and internal fragments of various sizes of the protein of interest.

Several techniques are known in the art for screening gene products of combinatorial libraries made by point mutations or truncation, and for screening cDNA libraries for gene products having a selected property. The most widely used techniques, which are amenable to high through-put analysis, for screening large gene libraries typically include cloning the gene library into replicable expression vectors, transforming appropriate cells with the resulting library of vectors, and expressing the combinatorial genes under conditions in which detection of a desired activity facilitates isolation of the vector encoding the gene whose product was detected. Recursive ensemble mutagenesis (REM), a technique which enhances the frequency of functional mutants in the libraries, can be used in combination with the screening assays to identify variants of a protein of the invention (Arkin and Yourvan, 1992, *Proc. Natl. Acad. Sci. USA* 89:7811-7815; Delgrave *et al.*, 1993, *Protein Engineering* 6(3):327-331).

Another aspect of the invention pertains to antibodies directed against a protein of the invention. In preferred embodiments, the antibodies specifically bind a marker protein or a fragment thereof. The terms "antibody" and "antibodies" as used interchangeably herein refer to immunoglobulin molecules as well as fragments and derivatives thereof that comprise an immunologically active portion of an immunoglobulin molecule, (*i.e.*, such a portion contains an antigen binding site which specifically binds an antigen, such as a marker protein, *e.g.*, an epitope of a marker protein). An antibody which specifically binds to a protein of the invention is an antibody which binds the protein, but does not substantially bind other molecules in a sample, *e.g.*, a biological sample, which naturally contains the protein. Examples of an immunologically active portion of an immunoglobulin molecule include, but are not limited to, single-chain antibodies (scAb), F(ab) and F(ab')₂ fragments.

An isolated protein of the invention or a fragment thereof can be used as an immunogen to generate antibodies. The full-length protein can be used or, alternatively, the invention provides antigenic peptide fragments for use as immunogens. The antigenic peptide of a protein of the invention comprises at least 8 (preferably 10, 15, 20, or 30 or more) amino acid residues of the amino acid sequence of one of the

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proteins of the invention, and encompasses at least one epitope of the protein such that an antibody raised against the peptide forms a specific immune complex with the protein. Preferred epitopes encompassed by the antigenic peptide are regions that are located on the surface of the protein, *e.g.*, hydrophilic regions. Hydrophobicity sequence analysis, hydrophilicity sequence analysis, or similar analyses can be used to identify hydrophilic regions. In preferred embodiments, an isolated marker protein or fragment thereof is used as an immunogen.

An immunogen typically is used to prepare antibodies by immunizing a suitable (*i.e.* immunocompetent) subject such as a rabbit, goat, mouse, or other mammal or vertebrate. An appropriate immunogenic preparation can contain, for example, recombinantly-expressed or chemically-synthesized protein or peptide. The preparation can further include an adjuvant, such as Freund's complete or incomplete adjuvant, or a similar immunostimulatory agent. Preferred immunogen compositions are those that contain no other human proteins such as, for example, immunogen compositions made using a non-human host cell for recombinant expression of a protein of the invention. In such a manner, the resulting antibody compositions have reduced or no binding of human proteins other than a protein of the invention.

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The invention provides polyclonal and monoclonal antibodies. The term "monoclonal antibody" or "monoclonal antibody composition", as used herein, refers to a population of antibody molecules that contain only one species of an antigen binding site capable of immunoreacting with a particular epitope. Preferred polyclonal and monoclonal antibody compositions are ones that have been selected for antibodies directed against a protein of the invention. Particularly preferred polyclonal and monoclonal antibody preparations are ones that contain only antibodies directed against a marker protein or fragment thereof.

Polyclonal antibodies can be prepared by immunizing a suitable subject with a protein of the invention as an immunogen. The antibody titer in the immunized subject can be monitored over time by standard techniques, such as with an enzyme linked immunosorbent assay (ELISA) using immobilized polypeptide. At an appropriate time after immunization, *e.g.*, when the specific antibody titers are highest, antibody-producing cells can be obtained from the subject and used to prepare monoclonal antibodies (mAb) by standard techniques, such as the hybridoma technique originally described by Kohler and Milstein (1975) *Nature* 256:495-497, the human B cell

hybridoma technique (see Kozbor et al., 1983, Immunol. Today 4:72), the EBV-hybridoma technique (see Cole et al., pp. 77-96 In Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, Inc., 1985) or trioma techniques. The technology for producing hybridomas is well known (see generally Current Protocols in Immunology, Coligan et al. ed., John Wiley & Sons, New York, 1994). Hybridoma cells producing a monoclonal antibody of the invention are detected by screening the hybridoma culture supernatants for antibodies that bind the polypeptide of interest, e.g., using a standard ELISA assay.

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Alternative to preparing monoclonal antibody-secreting hybridomas, a monoclonal antibody directed against a protein of the invention can be identified and isolated by screening a recombinant combinatorial immunoglobulin library (*e.g.*, an antibody phage display library) with the polypeptide of interest. Kits for generating and screening phage display libraries are commercially available (*e.g.*, the Pharmacia *Recombinant Phage Antibody System*, Catalog No. 27-9400-01; and the Stratagene *SurfZAP Phage Display Kit*, Catalog No. 240612). Additionally, examples of methods and reagents particularly amenable for use in generating and screening antibody display library can be found in, for example, U.S. Patent No. 5,223,409; PCT Publication No. WO 92/18619; PCT Publication No. WO 91/17271; PCT Publication No. WO 92/20791; PCT Publication No. WO 92/15679; PCT Publication No. WO 93/01288; PCT Publication No. WO 92/01047; PCT Publication No. WO 92/09690; PCT Publication No. WO 90/02809; Fuchs *et al.* (1991) *Bio/Technology* 9:1370-1372; Hay *et al.* (1992) *Hum. Antibod. Hybridomas* 3:81-85; Huse *et al.* (1989) *Science* 246:1275- 1281; Griffiths *et al.* (1993) *EMBO J.* 12:725-734.

The invention also provides recombinant antibodies that specifically bind a protein of the invention. In preferred embodiments, the recombinant antibodies specifically binds a marker protein or fragment thereof. Recombinant antibodies include, but are not limited to, chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, single-chain antibodies and multispecific antibodies. A chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region. (See, *e.g.*, Cabilly et al., U.S. Patent No. 4,816,567; and Boss et al., U.S. Patent No. 4,816,397, which are incorporated herein by reference in their entirety.) Single-chain antibodies have an

antigen binding site and consist of a single polypeptide. They can be produced by techniques known in the art, for example using methods described in Ladner *et. al* U.S. Pat. No. 4,946,778 (which is incorporated herein by reference in its entirety); Bird *et al.*, (1988) Science 242:423-426; Whitlow *et al.*, (1991) Methods in Enzymology 2:1-9; Whitlow *et al.*, (1991) Methods in Enzymology 2:97-105; and Huston *et al.*, (1991) Methods in Enzymology Molecular Design and Modeling: Concepts and Applications

Methods in Enzymology Molecular Design and Modeling: Concepts and Applications 203:46-88. Multi-specific antibodies are antibody molecules having at least two antigen-binding sites that specifically bind different antigens. Such molecules can be produced by techniques known in the art, for example using methods described in Segal,

U.S. Patent No. 4,676,980 (the disclosure of which is incorporated herein by reference in its entirety); Holliger et al., (1993) *Proc. Natl. Acad. Sci. USA* 90:6444-6448; *Whitlow et al.*, (1994) *Protein Eng.* 7:1017-1026 and U.S. Pat. No. 6,121,424.

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Humanized antibodies are antibody molecules from non-human species having one or more complementarity determining regions (CDRs) from the non-human species and a framework region from a human immunoglobulin molecule. (See, e.g., Queen, U.S. Patent No. 5,585,089, which is incorporated herein by reference in its entirety.) Humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art, for example using methods described in PCT Publication No. WO 87/02671; European Patent Application 184,187; European Patent Application 171,496; European Patent Application 173,494; PCT Publication No. WO 86/01533; U.S. Patent No. 4,816,567; European Patent Application 125,023; Better et al. (1988) Science 240:1041-1043; Liu et al. (1987) Proc. Natl. Acad. Sci. USA 84:3439-3443; Liu et al. (1987) J. Immunol. 139:3521-3526; Sun et al. (1987) Proc. Natl. Acad. Sci. USA 84:214-218; Nishimura et al. (1987) Cancer Res. 47:999-1005; Wood et al. (1985) Nature 314:446-449; and Shaw et al. (1988) J. Natl. Cancer Inst. 80:1553-1559); Morrison (1985) Science 229:1202-1207; Oi et al. (1986) Bio/Techniques 4:214; U.S. Patent 5,225,539; Jones et al. (1986) Nature 321:552-525; Verhoeyan et al. (1988) Science 239:1534; and Beidler et al. (1988) J. Immunol. 141:4053-4060.

More particularly, humanized antibodies can be produced, for example,
using transgenic mice which are incapable of expressing endogenous immunoglobulin
heavy and light chains genes, but which can express human heavy and light chain genes.
The transgenic mice are immunized in the normal fashion with a selected antigen, *e.g.*,
all or a portion of a polypeptide corresponding to a marker of the invention. Monoclonal

antibodies directed against the antigen can be obtained using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar (1995) *Int. Rev. Immunol.* 13:65-93). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, *e.g.*, U.S. Patent 5,625,126; U.S. Patent 5,633,425; U.S. Patent 5,569,825; U.S. Patent 5,661,016; and U.S. Patent 5,545,806. In addition, companies such as Abgenix, Inc. (Freemont, CA), can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

Completely human antibodies which recognize a selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, *e.g.*, a murine antibody, is used to guide the selection of a completely human antibody recognizing the same epitope (Jespers *et al.*, 1994, *Bio/technology* 12:899-903).

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The antibodies of the invention can be isolated after production (e.g., from the blood or serum of the subject) or synthesis and further purified by well-known techniques. For example, IgG antibodies can be purified using protein A chromatography. Antibodies specific for a protein of the invention can be selected or (e.g., partially purified) or purified by, e.g., affinity chromatography. For example, a recombinantly expressed and purified (or partially purified) protein of the invention is produced as described herein, and covalently or non-covalently coupled to a solid support such as, for example, a chromatography column. The column can then be used to affinity purify antibodies specific for the proteins of the invention from a sample containing antibodies directed against a large number of different epitopes, thereby generating a substantially purified antibody composition, i.e., one that is substantially free of contaminating antibodies. By a substantially purified antibody composition is meant, in this context, that the antibody sample contains at most only 30% (by dry weight) of contaminating antibodies directed against epitopes other than those of the desired protein of the invention, and preferably at most 20%, yet more preferably at most 10%, and most preferably at most 5% (by dry weight) of the sample is

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contaminating antibodies. A purified antibody composition means that at least 99% of the antibodies in the composition are directed against the desired protein of the invention.

In a preferred embodiment, the substantially purified antibodies of the invention may specifically bind to a signal peptide, a secreted sequence, an extracellular domain, a transmembrane or a cytoplasmic domain or cytoplasmic membrane of a protein of the invention. In a particularly preferred embodiment, the substantially purified antibodies of the invention specifically bind to a secreted sequence or an extracellular domain of the amino acid sequences of a protein of the invention. In a more preferred embodiment, the substantially purified antibodies of the invention specifically bind to a secreted sequence or an extracellular domain of the amino acid sequences of a marker protein.

An antibody directed against a protein of the invention can be used to isolate the protein by standard techniques, such as affinity chromatography or immunoprecipitation. Moreover, such an antibody can be used to detect the marker protein or fragment thereof (e.g., in a cellular lysate or cell supernatant) in order to evaluate the level and pattern of expression of the marker. The antibodies can also be used diagnostically to monitor protein levels in tissues or body fluids (e.g. in a cervicalassociated body fluid) as part of a clinical testing procedure, e.g., to, for example, determine the efficacy of a given treatment regimen. Detection can be facilitated by the use of an antibody derivative, which comprises an antibody of the invention coupled to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, β-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include ¹²⁵I, ¹³¹I, ³⁵S or ³H.

Antibodies of the invention may also be used as therapeutic agents in treating cancers. In a preferred embodiment, completely human antibodies of the invention are used for therapeutic treatment of human cancer patients, particularly those having an cervical cancer. In another preferred embodiment, antibodies that bind specifically to a marker protein or fragment thereof are used for therapeutic treatment. Further, such therapeutic antibody may be an antibody derivative or immunotoxin comprising an antibody conjugated to a therapeutic moiety such as a cytotoxin, a therapeutic agent or a radioactive metal ion. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include taxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclothosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine).

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The conjugated antibodies of the invention can be used for modifying a given biological response, for the drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as ribosome-inhibiting protein (see Better et al., U.S. Patent No. 6,146,631, the disclosure of which is incorporated herein in its entirety), abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor, alpha.-interferon, beta.-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophase colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

Techniques for conjugating such therapeutic moiety to antibodies are well known, see, e.g., Arnon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in Monoclonal Antibodies And Cancer Therapy, Reisfeld et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery", in Controlled Drug Delivery (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in Monoclonal Antibodies '84: Biological And Clinical Applications, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", Immunol. Rev., 62:119-58 (1982).

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Accordingly, in one aspect, the invention provides substantially purified antibodies, antibody fragments and derivatives, all of which specifically bind to a protein of the invention and preferably, a marker protein. In various embodiments, the substantially purified antibodies of the invention, or fragments or derivatives thereof, can be human, non-human, chimeric and/or humanized antibodies. In another aspect, the invention provides non-human antibodies, antibody fragments and derivatives, all of which specifically bind to a protein of the invention and preferably, a marker protein. Such non-human antibodies can be goat, mouse, sheep, horse, chicken, rabbit, or rat antibodies. Alternatively, the non-human antibodies of the invention can be chimeric and/or humanized antibodies. In addition, the non-human antibodies of the invention can be polyclonal antibodies or monoclonal antibodies. In still a further aspect, the invention provides monoclonal antibodies, antibody fragments and derivatives, all of which specifically bind to a protein of the invention and preferably, a marker protein. The monoclonal antibodies can be human, humanized, chimeric and/or non-human antibodies.

The invention also provides a kit containing an antibody of the invention conjugated to a detectable substance, and instructions for use. Still another aspect of the invention is a pharmaceutical composition comprising an antibody of the invention. In one embodiment, the pharmaceutical composition comprises an antibody of the invention and a pharmaceutically acceptable carrier.

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III. Recombinant Expression Vectors and Host Cells

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Another aspect of the invention pertains to vectors, preferably expression vectors, containing a nucleic acid encoding a marker protein (or a portion of such a protein). As used herein, the term "vector" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments can be ligated. Another type of vector is a viral vector, wherein additional DNA segments can be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (e.g., bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (e.g., non-episomal mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors, namely expression vectors, are capable of directing the expression of genes to which they are operably linked. In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids (vectors). However, the invention is intended to include such other forms of expression vectors, such as viral vectors (e.g., replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

The recombinant expression vectors of the invention comprise a nucleic acid of the invention in a form suitable for expression of the nucleic acid in a host cell. This means that the recombinant expression vectors include one or more regulatory sequences, selected on the basis of the host cells to be used for expression, which is operably linked to the nucleic acid sequence to be expressed. Within a recombinant expression vector, "operably linked" is intended to mean that the nucleotide sequence of interest is linked to the regulatory sequence(s) in a manner which allows for expression of the nucleotide sequence (e.g., in an in vitro transcription/translation system or in a host cell when the vector is introduced into the host cell). The term "regulatory sequence" is intended to include promoters, enhancers and other expression control elements (e.g., polyadenylation signals). Such regulatory sequences are described, for example, in Goeddel, Methods in Enzymology: Gene Expression Technology vol.185, Academic Press, San Diego, CA (1991). Regulatory sequences include those which direct constitutive expression of a nucleotide sequence in many types of host cell and

those which direct expression of the nucleotide sequence only in certain host cells (e.g., tissue-specific regulatory sequences). It will be appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired, and the like. The expression vectors of the invention can be introduced into host cells to thereby produce proteins or peptides, including fusion proteins or peptides, encoded by nucleic acids as described herein.

The recombinant expression vectors of the invention can be designed for expression of a marker protein or a segment thereof in prokaryotic (e.g., E. coli) or eukaryotic cells (e.g., insect cells {using baculovirus expression vectors}, yeast cells or mammalian cells). Suitable host cells are discussed further in Goeddel, supra. Alternatively, the recombinant expression vector can be transcribed and translated in vitro, for example using T7 promoter regulatory sequences and T7 polymerase.

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Expression of proteins in prokaryotes is most often carried out in E. coli with vectors containing constitutive or inducible promoters directing the expression of either fusion or non-fusion proteins. Fusion vectors add a number of amino acids to a protein encoded therein, usually to the amino terminus of the recombinant protein. Such fusion vectors typically serve three purposes: 1) to increase expression of recombinant protein; 2) to increase the solubility of the recombinant protein; and 3) to aid in the purification of the recombinant protein by acting as a ligand in affinity purification. Often, in fusion expression vectors, a proteolytic cleavage site is introduced at the junction of the fusion moiety and the recombinant protein to enable separation of the recombinant protein from the fusion moiety subsequent to purification of the fusion protein. Such enzymes, and their cognate recognition sequences, include Factor Xa, thrombin and enterokinase. Typical fusion expression vectors include pGEX (Pharmacia Biotech Inc; Smith and Johnson, 1988, Gene 67:31-40), pMAL (New England Biolabs, Beverly, MA) and pRIT5 (Pharmacia, Piscataway, NJ) which fuse glutathione S-transferase (GST), maltose E binding protein, or protein A, respectively, to the target recombinant protein.

Examples of suitable inducible non-fusion *E. coli* expression vectors include pTrc (Amann *et al.*, 1988, *Gene* 69:301-315) and pET 11d (Studier *et al.*, p. 60-89, In *Gene Expression Technology: Methods in Enzymology* vol.185, Academic Press, San Diego, CA, 1991). Target gene expression from the pTrc vector relies on host RNA

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polymerase transcription from a hybrid trp-lac fusion promoter. Target gene expression from the pET 11d vector relies on transcription from a T7 gn10-lac fusion promoter mediated by a co-expressed viral RNA polymerase (T7 gn1). This viral polymerase is supplied by host strains BL21(DE3) or HMS174(DE3) from a resident prophage harboring a T7 gn1 gene under the transcriptional control of the lacUV 5 promoter.

One strategy to maximize recombinant protein expression in *E. coli* is to express the protein in a host bacteria with an impaired capacity to proteolytically cleave the recombinant protein (Gottesman, p. 119-128, In *Gene Expression Technology: Methods in Enzymology* vol. 185, Academic Press, San Diego, CA, 1990. Another strategy is to alter the nucleic acid sequence of the nucleic acid to be inserted into an expression vector so that the individual codons for each amino acid are those preferentially utilized in *E. coli* (Wada *et al.*, 1992, *Nucleic Acids Res.* 20:2111-2118). Such alteration of nucleic acid sequences of the invention can be carried out by standard DNA synthesis techniques.

In another embodiment, the expression vector is a yeast expression vector. Examples of vectors for expression in yeast *S. cerevisiae* include pYepSec1 (Baldari *et al.*, 1987, *EMBO J.* 6:229-234), pMFa (Kurjan and Herskowitz, 1982, *Cell* 30:933-943), pJRY88 (Schultz *et al.*, 1987, *Gene* 54:113-123), pYES2 (Invitrogen Corporation, San Diego, CA), and pPicZ (Invitrogen Corp, San Diego, CA).

Alternatively, the expression vector is a baculovirus expression vector. Baculovirus vectors available for expression of proteins in cultured insect cells (*e.g.*, Sf 9 cells) include the pAc series (Smith *et al.*, 1983, *Mol. Cell Biol.* 3:2156-2165) and the pVL series (Lucklow and Summers, 1989, *Virology* 170:31-39).

In yet another embodiment, a nucleic acid of the invention is expressed in mammalian cells using a mammalian expression vector. Examples of mammalian expression vectors include pCDM8 (Seed, 1987, *Nature* 329:840) and pMT2PC (Kaufman *et al.*, 1987, *EMBO J.* 6:187-195). When used in mammalian cells, the expression vector's control functions are often provided by viral regulatory elements. For example, commonly used promoters are derived from polyoma, Adenovirus 2, cytomegalovirus and Simian Virus 40. For other suitable expression systems for both prokaryotic and eukaryotic cells see chapters 16 and 17 of Sambrook *et al.*, *supra*.

In another embodiment, the recombinant mammalian expression vector is capable of directing expression of the nucleic acid preferentially in a particular cell type (e.g., tissue-specific regulatory elements are used to express the nucleic acid). Tissuespecific regulatory elements are known in the art. Non-limiting examples of suitable tissue-specific promoters include the albumin promoter (liver-specific; Pinkert et al., 1987, Genes Dev. 1:268-277), lymphoid-specific promoters (Calame and Eaton, 1988, Adv. Immunol. 43:235-275), in particular promoters of T cell receptors (Winoto and Baltimore, 1989, EMBO J. 8:729-733) and immunoglobulins (Banerji et al., 1983, Cell 33:729-740; Queen and Baltimore, 1983, Cell 33:741-748), neuron-specific promoters (e.g., the neurofilament promoter; Byrne and Ruddle, 1989, Proc. Natl. Acad. Sci. USA 86:5473-5477), pancreas-specific promoters (Edlund et al., 1985, Science 230:912-916), and mammary gland-specific promoters (e.g., milk whey promoter; U.S. Patent No. 4,873,316 and European Application Publication No. 264,166). Developmentallyregulated promoters are also encompassed, for example the murine hox promoters (Kessel and Gruss, 1990, Science 249:374-379) and the α-fetoprotein promoter (Camper and Tilghman, 1989, Genes Dev. 3:537-546).

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The invention further provides a recombinant expression vector comprising a DNA molecule of the invention cloned into the expression vector in an antisense orientation. That is, the DNA molecule is operably linked to a regulatory sequence in a manner which allows for expression (by transcription of the DNA molecule) of an RNA molecule which is antisense to the mRNA encoding a polypeptide of the invention. Regulatory sequences operably linked to a nucleic acid cloned in the antisense orientation can be chosen which direct the continuous expression of the antisense RNA molecule in a variety of cell types, for instance viral promoters and/or enhancers, or regulatory sequences can be chosen which direct constitutive, tissue-specific or cell type specific expression of antisense RNA. The antisense expression vector can be in the form of a recombinant plasmid, phagemid, or attenuated virus in which antisense nucleic acids are produced under the control of a high efficiency regulatory region, the activity of which can be determined by the cell type into which the vector is introduced. For a discussion of the regulation of gene expression using antisense genes see Weintraub *et al.*, 1986, *Trends in Genetics*, Vol. 1(1).

Another aspect of the invention pertains to host cells into which a recombinant expression vector of the invention has been introduced. The terms "host cell" and "recombinant host cell" are used interchangeably herein. It is understood that such terms refer not only to the particular subject cell but to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

A host cell can be any prokaryotic (e.g., E. coli) or eukaryotic cell (e.g., insect cells, yeast or mammalian cells).

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Vector DNA can be introduced into prokaryotic or eukaryotic cells via conventional transformation or transfection techniques. As used herein, the terms "transformation" and "transfection" are intended to refer to a variety of art-recognized techniques for introducing foreign nucleic acid into a host cell, including calcium phosphate or calcium chloride co-precipitation, DEAE-dextran-mediated transfection, lipofection, or electroporation. Suitable methods for transforming or transfecting host cells can be found in Sambrook, *et al.* (*supra*), and other laboratory manuals.

For stable transfection of mammalian cells, it is known that, depending upon the expression vector and transfection technique used, only a small fraction of cells may integrate the foreign DNA into their genome. In order to identify and select these integrants, a gene that encodes a selectable marker (e.g., for resistance to antibiotics) is generally introduced into the host cells along with the gene of interest. Preferred selectable markers include those which confer resistance to drugs, such as G418, hygromycin and methotrexate. Cells stably transfected with the introduced nucleic acid can be identified by drug selection (e.g., cells that have incorporated the selectable marker will survive, while the other cells die).

A host cell of the invention, such as a prokaryotic or eukaryotic host cell in culture, can be used to produce a marker protein or a segment thereof. Accordingly, the invention further provides methods for producing a marker protein or a segment thereof using the host cells of the invention. In one embodiment, the method comprises culturing the host cell of the invention (into which a recombinant expression vector encoding a marker protein or a segment thereof has been introduced) in a suitable medium such that the is produced. In another embodiment, the method further

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comprises isolating the marker protein or a segment thereof from the medium or the host cell.

The host cells of the invention can also be used to produce nonhuman transgenic animals. For example, in one embodiment, a host cell of the invention is a fertilized oocyte or an embryonic stem cell into which a sequences encoding a marker protein or a segment thereof have been introduced. Such host cells can then be used to create non-human transgenic animals in which exogenous sequences encoding a marker protein of the invention have been introduced into their genome or homologous recombinant animals in which endogenous gene(s) encoding a marker protein have been altered. Such animals are useful for studying the function and/or activity of the marker protein and for identifying and/or evaluating modulators of marker protein. As used herein, a "transgenic animal" is a non-human animal, preferably a mammal, more preferably a rodent such as a rat or mouse, in which one or more of the cells of the animal includes a transgene. Other examples of transgenic animals include non-human 15 primates, sheep, dogs, cows, goats, chickens, amphibians, etc. A transgene is exogenous DNA which is integrated into the genome of a cell from which a transgenic animal develops and which remains in the genome of the mature animal, thereby directing the expression of an encoded gene product in one or more cell types or tissues of the transgenic animal. As used herein, an "homologous recombinant animal" is a nonhuman animal, preferably a mammal, more preferably a mouse, in which an endogenous gene has been altered by homologous recombination between the endogenous gene and an exogenous DNA molecule introduced into a cell of the animal, e.g., an embryonic cell of the animal, prior to development of the animal.

A transgenic animal of the invention can be created by introducing a nucleic acid encoding a marker protein into the male pronuclei of a fertilized oocyte, e.g., by microinjection, retroviral infection, and allowing the oocyte to develop in a pseudopregnant female foster animal. Intronic sequences and polyadenylation signals can also be included in the transgene to increase the efficiency of expression of the transgene. A tissue-specific regulatory sequence(s) can be operably linked to the transgene to direct expression of the polypeptide of the invention to particular cells. Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009, U.S. Patent No.

4,873,191 and in Hogan, *Manipulating the Mouse Embryo*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986. Similar methods are used for production of other transgenic animals. A transgenic founder animal can be identified based upon the presence of the transgene in its genome and/or expression of mRNA encoding the transgene in tissues or cells of the animals. A transgenic founder animal can then be used to breed additional animals carrying the transgene. Moreover, transgenic animals carrying the transgene can further be bred to other transgenic animals carrying other transgenes.

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To create an homologous recombinant animal, a vector is prepared which contains at least a portion of a gene encoding a marker protein into which a deletion, addition or substitution has been introduced to thereby alter, e.g., functionally disrupt, the gene. In a preferred embodiment, the vector is designed such that, upon homologous recombination, the endogenous gene is functionally disrupted (i.e., no longer encodes a functional protein; also referred to as a "knock out" vector). Alternatively, the vector can be designed such that, upon homologous recombination, the endogenous gene is mutated or otherwise altered but still encodes functional protein (e.g., the upstream regulatory region can be altered to thereby alter the expression of the endogenous protein). In the homologous recombination vector, the altered portion of the gene is flanked at its 5' and 3' ends by additional nucleic acid of the gene to allow for homologous recombination to occur between the exogenous gene carried by the vector and an endogenous gene in an embryonic stem cell. The additional flanking nucleic acid sequences are of sufficient length for successful homologous recombination with the endogenous gene. Typically, several kilobases of flanking DNA (both at the 5' and 3' ends) are included in the vector (see, e.g., Thomas and Capecchi, 1987, Cell 51:503 for a description of homologous recombination vectors). The vector is introduced into an embryonic stem cell line (e.g., by electroporation) and cells in which the introduced gene has homologously recombined with the endogenous gene are selected (see, e.g., Li et al., 1992, Cell 69:915). The selected cells are then injected into a blastocyst of an animal (e.g., a mouse) to form aggregation chimeras (see, e.g., Bradley, Teratocarcinomas and Embryonic Stem Cells: A Practical Approach, Robertson, Ed., IRL, Oxford, 1987, pp. 113-152). A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term. Progeny harboring the homologously recombined DNA in their germ cells can be used to breed

animals in which all cells of the animal contain the homologously recombined DNA by germline transmission of the transgene. Methods for constructing homologous recombination vectors and homologous recombinant animals are described further in Bradley (1991) *Current Opinion in Bio/Technology* 2:823-829 and in PCT Publication NOS. WO 90/11354, WO 91/01140, WO 92/0968, and WO 93/04169.

In another embodiment, transgenic non-human animals can be produced which contain selected systems which allow for regulated expression of the transgene. One example of such a system is the *cre/loxP* recombinase system of bacteriophage P1. For a description of the *cre/loxP* recombinase system, see, *e.g.*, Lakso *et al.* (1992) *Proc. Natl. Acad. Sci. USA* 89:6232-6236. Another example of a recombinase system is the FLP recombinase system of *Saccharomyces cerevisiae* (O'Gorman *et al.*, 1991, *Science* 251:1351-1355). If a *cre/loxP* recombinase system is used to regulate expression of the transgene, animals containing transgenes encoding both the *Cre* recombinase and a selected protein are required. Such animals can be provided through the construction of "double" transgenic animals, *e.g.*, by mating two transgenic animals, one containing a transgene encoding a selected protein and the other containing a transgene encoding a recombinase.

Clones of the non-human transgenic animals described herein can also be produced according to the methods described in Wilmut *et al.* (1997) *Nature* 385:810-813 and PCT Publication NOS. WO 97/07668 and WO 97/07669.

IV. Pharmaceutical Compositions

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The nucleic acid molecules, polypeptides, and antibodies (also referred to herein as "active compounds") of the invention can be incorporated into pharmaceutical compositions suitable for administration. Such compositions typically comprise the nucleic acid molecule, protein, or antibody and a pharmaceutically acceptable carrier. As used herein the language "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is

contemplated. Supplementary active compounds can also be incorporated into the compositions.

The invention includes methods for preparing pharmaceutical compositions for modulating the expression or activity of a marker nucleic acid or protein . Such methods comprise formulating a pharmaceutically acceptable carrier with an agent which modulates expression or activity of a marker nucleic acid or protein. Such compositions can further include additional active agents. Thus, the invention further includes methods for preparing a pharmaceutical composition by formulating a pharmaceutically acceptable carrier with an agent which modulates expression or activity of a marker nucleic acid or protein and one or more additional active compounds.

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The invention also provides methods (also referred to herein as "screening assays") for identifying modulators, *i.e.*, candidate or test compounds or agents (*e.g.*, peptides, peptidomimetics, peptoids, small molecules or other drugs) which (a) bind to the marker, or (b) have a modulatory (*e.g.*, stimulatory or inhibitory) effect on the activity of the marker or, more specifically, (c) have a modulatory effect on the interactions of the marker with one or more of its natural substrates (*e.g.*, peptide, protein, hormone, co-factor, or nucleic acid), or (d) have a modulatory effect on the expression of the marker. Such assays typically comprise a reaction between the marker and one or more assay components. The other components may be either the test compound itself, or a combination of test compound and a natural binding partner of the marker.

The test compounds of the present invention may be obtained from any available source, including systematic libraries of natural and/or synthetic compounds.

Test compounds may also be obtained by any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; peptoid libraries (libraries of molecules having the functionalities of peptides, but with a novel, non-peptide backbone which are resistant to enzymatic degradation but which nevertheless remain bioactive; see, e.g., Zuckermann et al., 1994, J. Med. Chem.

37:2678-85); spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the 'one-bead one-compound' library method; and synthetic library methods using affinity chromatography selection. The biological library and peptoid library approaches are limited to peptide libraries, while

the other four approaches are applicable to peptide, non-peptide oligomer or small molecule libraries of compounds (Lam, 1997, *Anticancer Drug Des.* 12:145).

Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt et al. (1993) Proc. Natl. Acad. Sci. U.S.A. 90:6909; Erb et al. (1994) Proc. Natl. Acad. Sci. USA 91:11422; Zuckermann et al. (1994). J. Med. Chem. 37:2678; Cho et al. (1993) Science 261:1303; Carrell et al. (1994) Angew. Chem. Int. Ed. Engl. 33:2059; Carell et al. (1994) Angew. Chem. Int. Ed. Engl. 33:2061; and in Gallop et al. (1994) J. Med. Chem. 37:1233.

Libraries of compounds may be presented in solution (e.g., Houghten, 1992, Biotechniques 13:412-421), or on beads (Lam, 1991, Nature 354:82-84), chips (Fodor, 1993, Nature 364:555-556), bacteria and/or spores, (Ladner, USP 5,223,409), plasmids (Cull et al, 1992, Proc Natl Acad Sci USA 89:1865-1869) or on phage (Scott and Smith, 1990, Science 249:386-390; Devlin, 1990, Science 249:404-406; Cwirla et al, 1990, Proc. Natl. Acad. Sci. 87:6378-6382; Felici, 1991, J. Mol. Biol. 222:301-310; Ladner, supra.).

In one embodiment, the invention provides assays for screening candidate or test compounds which are substrates of a protein encoded by or corresponding to a marker or biologically active portion thereof. In another embodiment, the invention provides assays for screening candidate or test compounds which bind to a protein encoded by or corresponding to a marker or biologically active portion thereof. Determining the ability of the test compound to directly bind to a protein can be accomplished, for example, by coupling the compound with a radioisotope or enzymatic label such that binding of the compound to the marker can be determined by detecting the labeled marker compound in a complex. For example, compounds (*e.g.*, marker substrates) can be labeled with ¹²⁵I, ³⁵S, ¹⁴C, or ³H, either directly or indirectly, and the radioisotope detected by direct counting of radioemission or by scintillation counting. Alternatively, assay components can be enzymatically labeled with, for example, horseradish peroxidase, alkaline phosphatase, or luciferase, and the enzymatic label detected by determination of conversion of an appropriate substrate to product.

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In another embodiment, the invention provides assays for screening candidate or test compounds which modulate the expression of a marker or the activity of a protein encoded by or corresponding to a marker, or a biologically active portion

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thereof. In all likelihood, the protein encoded by or corresponding to the marker can, *in vivo*, interact with one or more molecules, such as but not limited to, peptides, proteins, hormones, cofactors and nucleic acids. For the purposes of this discussion, such cellular and extracellular molecules are referred to herein as "binding partners" or marker "substrate".

One necessary embodiment of the invention in order to facilitate such screening is the use of a protein encoded by or corresponding to marker to identify the protein's natural *in vivo* binding partners. There are many ways to accomplish this which are known to one skilled in the art. One example is the use of the marker protein as "bait protein" in a two-hybrid assay or three-hybrid assay (see, *e.g.*, U.S. Patent No. 5,283,317; Zervos *et al*, 1993, *Cell* 72:223-232; Madura *et al*, 1993, *J. Biol. Chem.* 268:12046-12054; Bartel *et al*,1993, *Biotechniques* 14:920-924; Iwabuchi *et al*, 1993 *Oncogene* 8:1693-1696; Brent WO94/10300) in order to identify other proteins which bind to or interact with the marker (binding partners) and, therefore, are possibly involved in the natural function of the marker. Such marker binding partners are also likely to be involved in the propagation of signals by the marker protein or downstream elements of a marker protein-mediated signaling pathway. Alternatively, such marker protein binding partners may also be found to be inhibitors of the marker protein.

The two-hybrid system is based on the modular nature of most transcription factors, which consist of separable DNA-binding and activation domains. Briefly, the assay utilizes two different DNA constructs. In one construct, the gene that encodes a marker protein fused to a gene encoding the DNA binding domain of a known transcription factor (e.g., GAL-4). In the other construct, a DNA sequence, from a library of DNA sequences, that encodes an unidentified protein ("prey" or "sample") is fused to a gene that codes for the activation domain of the known transcription factor. If the "bait" and the "prey" proteins are able to interact, in vivo, forming a marker-dependent complex, the DNA-binding and activation domains of the transcription factor are brought into close proximity. This proximity allows transcription of a reporter gene (e.g., LacZ) which is operably linked to a transcriptional regulatory site responsive to the transcription factor. Expression of the reporter gene can be readily detected and cell colonies containing the functional transcription factor can be isolated and used to obtain the cloned gene which encodes the protein which interacts with the marker protein.

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In a further embodiment, assays may be devised through the use of the invention for the purpose of identifying compounds which modulate (e.g., affect either positively or negatively) interactions between a marker protein and its substrates and/or binding partners. Such compounds can include, but are not limited to, molecules such as antibodies, peptides, hormones, oligonucleotides, nucleic acids, and analogs thereof. Such compounds may also be obtained from any available source, including systematic libraries of natural and/or synthetic compounds. The preferred assay components for use in this embodiment is an cervical cancer marker protein identified herein, the known binding partner and/or substrate of same, and the test compound. Test compounds can be supplied from any source.

The basic principle of the assay systems used to identify compounds that interfere with the interaction between the marker protein and its binding partner involves preparing a reaction mixture containing the marker protein and its binding partner under conditions and for a time sufficient to allow the two products to interact and bind, thus forming a complex. In order to test an agent for inhibitory activity, the reaction mixture is prepared in the presence and absence of the test compound. The test compound can be initially included in the reaction mixture, or can be added at a time subsequent to the addition of the marker protein and its binding partner. Control reaction mixtures are incubated without the test compound or with a placebo. The formation of any complexes between the marker protein and its binding partner is then detected. The formation of a complex in the control reaction, but less or no such formation in the reaction mixture containing the test compound, indicates that the compound interferes with the interaction of the marker protein and its binding partner. Conversely, the formation of more complex in the presence of compound than in the control reaction indicates that the compound may enhance interaction of the marker protein and its binding partner.

The assay for compounds that interfere with the interaction of the marker protein with its binding partner may be conducted in a heterogeneous or homogeneous format. Heterogeneous assays involve anchoring either the marker protein or its binding partner onto a solid phase and detecting complexes anchored to the solid phase at the end of the reaction. In homogeneous assays, the entire reaction is carried out in a liquid phase. In either approach, the order of addition of reactants can be varied to obtain different information about the compounds being tested. For example, test compounds

that interfere with the interaction between the marker proteins and the binding partners (e.g., by competition) can be identified by conducting the reaction in the presence of the test substance, i.e., by adding the test substance to the reaction mixture prior to or simultaneously with the marker and its interactive binding partner. Alternatively, test compounds that disrupt preformed complexes, e.g., compounds with higher binding constants that displace one of the components from the complex, can be tested by adding the test compound to the reaction mixture after complexes have been formed. The various formats are briefly described below.

In a heterogeneous assay system, either the marker protein or its binding partner is anchored onto a solid surface or matrix, while the other corresponding non-anchored component may be labeled, either directly or indirectly. In practice, microtitre plates are often utilized for this approach. The anchored species can be immobilized by a number of methods, either non-covalent or covalent, that are typically well known to one who practices the art. Non-covalent attachment can often be accomplished simply by coating the solid surface with a solution of the marker protein or its binding partner and drying. Alternatively, an immobilized antibody specific for the assay component to be anchored can be used for this purpose. Such surfaces can often be prepared in advance and stored.

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In related embodiments, a fusion protein can be provided which adds a domain that allows one or both of the assay components to be anchored to a matrix. For example, glutathione-S-transferase/marker fusion proteins or glutathione-S-transferase/binding partner can be adsorbed onto glutathione sepharose beads (Sigma Chemical, St. Louis, MO) or glutathione derivatized microtiter plates, which are then combined with the test compound or the test compound and either the non-adsorbed marker or its binding partner, and the mixture incubated under conditions conducive to complex formation (*e.g.*, physiological conditions). Following incubation, the beads or microtiter plate wells are washed to remove any unbound assay components, the immobilized complex assessed either directly or indirectly, for example, as described above. Alternatively, the complexes can be dissociated from the matrix, and the level of marker binding or activity determined using standard techniques.

Other techniques for immobilizing proteins on matrices can also be used in the screening assays of the invention. For example, either a marker protein or a marker protein binding partner can be immobilized utilizing conjugation of biotin and streptavidin. Biotinylated marker protein or target molecules can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques known in the art (e.g., biotinylation kit, Pierce Chemicals, Rockford, IL), and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical). In certain embodiments, the protein-immobilized surfaces can be prepared in advance and stored.

In order to conduct the assay, the corresponding partner of the immobilized assay component is exposed to the coated surface with or without the test compound. After the reaction is complete, unreacted assay components are removed (e.g., by washing) and any complexes formed will remain immobilized on the solid surface. The detection of complexes anchored on the solid surface can be accomplished in a number of ways. Where the non-immobilized component is pre-labeled, the detection of label immobilized on the surface indicates that complexes were formed. Where the non-immobilized component is not pre-labeled, an indirect label can be used to detect complexes anchored on the surface; e.g., using a labeled antibody specific for the initially non-immobilized species (the antibody, in turn, can be directly labeled or indirectly labeled with, e.g., a labeled anti-Ig antibody). Depending upon the order of addition of reaction components, test compounds which modulate (inhibit or enhance) complex formation or which disrupt preformed complexes can be detected.

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In an alternate embodiment of the invention, a homogeneous assay may be used. This is typically a reaction, analogous to those mentioned above, which is conducted in a liquid phase in the presence or absence of the test compound. The formed complexes are then separated from unreacted components, and the amount of complex formed is determined. As mentioned for heterogeneous assay systems, the order of addition of reactants to the liquid phase can yield information about which test compounds modulate (inhibit or enhance) complex formation and which disrupt preformed complexes.

In such a homogeneous assay, the reaction products may be separated from unreacted assay components by any of a number of standard techniques, including but not limited to: differential centrifugation, chromatography, electrophoresis and immunoprecipitation. In differential centrifugation, complexes of molecules may be separated from uncomplexed molecules through a series of centrifugal steps, due to the different sedimentation equilibria of complexes based on their different sizes and densities (see, for example, Rivas, G., and Minton, A.P., *Trends Biochem Sci* 1993

Aug;18(8):284-7). Standard chromatographic techniques may also be utilized to separate complexed molecules from uncomplexed ones. For example, gel filtration chromatography separates molecules based on size, and through the utilization of an appropriate gel filtration resin in a column format, for example, the relatively larger complex may be separated from the relatively smaller uncomplexed components. Similarly, the relatively different charge properties of the complex as compared to the uncomplexed molecules may be exploited to differentially separate the complex from the remaining individual reactants, for example through the use of ion-exchange chromatography resins. Such resins and chromatographic techniques are well known to one skilled in the art (see, e.g., Heegaard, 1998, J Mol. Recognit. 11:141-148; Hage and Tweed, 1997, J. Chromatogr. B. Biomed. Sci. Appl., 699:499-525). Gel electrophoresis may also be employed to separate complexed molecules from unbound species (see, e.g., Ausubel et al (eds.), In: Current Protocols in Molecular Biology, J. Wiley & Sons, New York. 1999). In this technique, protein or nucleic acid complexes are separated based on size or charge, for example. In order to maintain the binding interaction during the electrophoretic process, nondenaturing gels in the absence of reducing agent are typically preferred, but conditions appropriate to the particular interactants will be well known to one skilled in the art. Immunoprecipitation is another common technique utilized for the isolation of a protein-protein complex from solution (see, e.g., Ausubel et al (eds.), In: Current Protocols in Molecular Biology, J. Wiley & Sons, New York. 1999). In this technique, all proteins binding to an antibody specific to one of the binding molecules are precipitated from solution by conjugating the antibody to a polymer bead that may be readily collected by centrifugation. The bound assay components are released from the beads (through a specific proteolysis event or other technique well known in the art which will not disturb the protein-protein interaction in the complex), and a second immunoprecipitation step is performed, this time utilizing antibodies specific for the correspondingly different interacting assay component. In this manner, only formed complexes should remain attached to the beads. Variations in complex formation in both the presence and the absence of a test compound can be compared, thus offering information about the ability of the compound to modulate interactions between the marker protein and its binding partner.

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Also within the scope of the present invention are methods for direct detection of interactions between the marker protein and its natural binding partner and/or a test compound in a homogeneous or heterogeneous assay system without further sample manipulation. For example, the technique of fluorescence energy transfer may be utilized (see, e.g., Lakowicz et al, U.S. Patent No. 5,631,169; Stavrianopoulos et al, U.S. Patent No. 4,868,103). Generally, this technique involves the addition of a fluorophore label on a first 'donor' molecule (e.g., marker or test compound) such that its emitted fluorescent energy will be absorbed by a fluorescent label on a second, 'acceptor' molecule (e.g., marker or test compound), which in turn is able to fluoresce due to the absorbed energy. Alternately, the 'donor' protein molecule may simply utilize the natural fluorescent energy of tryptophan residues. Labels are chosen that emit different wavelengths of light, such that the 'acceptor' molecule label may be differentiated from that of the 'donor'. Since the efficiency of energy transfer between the labels is related to the distance separating the molecules, spatial relationships between the molecules can be assessed. In a situation in which binding occurs between the molecules, the fluorescent emission of the 'acceptor' molecule label in the assay should be maximal. An FET binding event can be conveniently measured through standard fluorometric detection means well known in the art (e.g., using a fluorimeter). A test substance which either enhances or hinders participation of one of the species in the preformed complex will result in the generation of a signal variant to that of background. In this way, test substances that modulate interactions between a marker and its binding partner can be identified in controlled assays.

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In another embodiment, modulators of marker expression are identified in a method wherein a cell is contacted with a candidate compound and the expression of marker mRNA or protein in the cell, is determined. The level of expression of marker mRNA or protein in the presence of the candidate compound is compared to the level of expression of marker mRNA or protein in the absence of the candidate compound. The candidate compound can then be identified as a modulator of marker expression based on this comparison. For example, when expression of marker mRNA or protein is greater (statistically significantly greater) in the presence of the candidate compound than in its absence, the candidate compound is identified as a stimulator of marker mRNA or protein expression. Conversely, when expression of marker mRNA or protein is less (statistically significantly less) in the presence of the candidate compound

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than in its absence, the candidate compound is identified as an inhibitor of marker mRNA or protein expression. The level of marker mRNA or protein expression in the cells can be determined by methods described herein for detecting marker mRNA or protein.

In another aspect, the invention pertains to a combination of two or more of the assays described herein. For example, a modulating agent can be identified using a cell-based or a cell free assay, and the ability of the agent to modulate the activity of a marker protein can be further confirmed *in vivo*, *e.g.*, in a whole animal model for cellular transformation and/or tumorigenesis.

This invention further pertains to novel agents identified by the above-described screening assays. Accordingly, it is within the scope of this invention to further use an agent identified as described herein in an appropriate animal model. For example, an agent identified as described herein (*e.g.*, a marker modulating agent, an antisense marker nucleic acid molecule, a marker-specific antibody, or a marker-binding partner) can be used in an animal model to determine the efficacy, toxicity, or side effects of treatment with such an agent. Alternatively, an agent identified as described herein can be used in an animal model to determine the mechanism of action of such an agent. Furthermore, this invention pertains to uses of novel agents identified by the above-described screening assays for treatments as described herein.

It is understood that appropriate doses of small molecule agents and protein or polypeptide agents depends upon a number of factors within the knowledge of the ordinarily skilled physician, veterinarian, or researcher. The dose(s) of these agents will vary, for example, depending upon the identity, size, and condition of the subject or sample being treated, further depending upon the route by which the composition is to be administered, if applicable, and the effect which the practitioner desires the agent to have upon the nucleic acid or polypeptide of the invention. Exemplary doses of a small molecule include milligram or microgram amounts per kilogram of subject or sample weight (e.g. about 1 microgram per kilogram to about 500 milligrams per kilogram, about 1 micrograms per kilogram to about 5 milligrams per kilogram, or about 1 microgram per kilogram to about 50 micrograms per kilogram). Exemplary doses of a protein or polypeptide include gram, milligram or microgram amounts per kilogram of subject or sample weight (e.g. about 1 microgram per kilogram to about 5 grams per kilogram, or sample weight (e.g. about 1 microgram per kilogram to about 5 grams per kilogram, about 100 micrograms per kilogram to about 500 milligrams per kilogram, or

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about 1 milligram per kilogram to about 50 milligrams per kilogram). It is furthermore understood that appropriate doses of one of these agents depend upon the potency of the agent with respect to the expression or activity to be modulated. Such appropriate doses can be determined using the assays described herein. When one or more of these agents is to be administered to an animal (e.g. a human) in order to modulate expression or activity of a polypeptide or nucleic acid of the invention, a physician, veterinarian, or researcher can, for example, prescribe a relatively low dose at first, subsequently increasing the dose until an appropriate response is obtained. In addition, it is understood that the specific dose level for any particular animal subject will depend upon a variety of factors including the activity of the specific agent employed, the age, body weight, general health, gender, and diet of the subject, the time of administration, the route of administration, the rate of excretion, any drug combination, and the degree of expression or activity to be modulated.

A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, e.g., intravenous, intradermal, subcutaneous, oral (e.g., inhalation), transdermal (topical), transmucosal, and rectal administration.

Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampules, disposable syringes or multiple dose vials made of glass or plastic.

Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL (BASF; Parsippany, NJ) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy

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syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound (e.g., a polypeptide or antibody) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium, and then incorporating the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed.

Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches, and the like can contain any of the following ingredients, or compounds of a similar nature: a

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binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

For administration by inhalation, the compounds are delivered in the form of an aerosol spray from a pressurized container or dispenser which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebulizer.

Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

The compounds can also be prepared in the form of suppositories (e.g., with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems.

Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid.

Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes having monoclonal antibodies incorporated therein or thereon) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811.

It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the 5

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subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals.

For antibodies, the preferred dosage is 0.1 mg/kg to 100 mg/kg of body weight (generally 10 mg/kg to 20 mg/kg). If the antibody is to act in the brain, a dosage of 50 mg/kg to 100 mg/kg is usually appropriate. Generally, partially human antibodies and fully human antibodies have a longer half-life within the human body than other antibodies. Accordingly, lower dosages and less frequent administration is often possible. Modifications such as lipidation can be used to stabilize antibodies and to enhance uptake and tissue penetration (e.g., into the cervical epithelium). A method for lipidation of antibodies is described by Cruikshank et al. (1997) J. Acquired Immune Deficiency Syndromes and Human Retrovirology 14:193.

The invention also provides vaccine compositions for the prevention and/or treatment of cervical cancer. The invention provides cervical cancer vaccine compositions in which a protein of a marker of Table 1, or a combination of proteins of the markers of Table 1, are introduced into a subject in order to stimulate an immune response against the cervical cancer. The invention also provides cervical cancer vaccine compositions in which a gene expression construct, which expresses a marker or fragment of a marker identified in Table 1, is introduced into the subject such that a protein or fragment of a protein encoded by a marker of Table 1 is produced by transfected cells in the subject at a higher than normal level and elicits an immune response.

In one embodiment, a cervical cancer vaccine is provided and employed as an immunotherapeutic agent for the prevention of cervical cancer. In another embodiment, a cervical cancer vaccine is provided and employed as an immunotherapeutic agent for the treatment of cervical cancer.

By way of example, a cervical cancer vaccine comprised of the proteins of the markers of Table 1, may be employed for the prevention and/or treatment of cervical cancer in a subject by administering the vaccine by a variety of routes, *e.g.*, intradermally, subcutaneously, or intramuscularly. In addition, the cervical cancer

vaccine can be administered together with adjuvants and/or immunomodulators to boost the activity of the vaccine and the subject's response. In one embodiment, devices and/or compositions containing the vaccine, suitable for sustained or intermittent release could be, implanted in the body or topically applied thereto for the relatively slow release of such materials into the body. The cervical cancer vaccine can be introduced along with immunomodulatory compounds, which can alter the type of immune response produced in order to produce a response which will be more effective in eliminating the cancer.

In another embodiment, a cervical cancer vaccine comprised of an expression construct of the markers of Table 1, may be introduced by injection into muscle or by coating onto microprojectiles and using a device designed for the purpose to fire the projectiles at high speed into the skin. The cells of the subject will then express the protein(s) or fragments of proteins of the markers of Table 1 and induce an immune

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response. In addition, the cervical cancer vaccine may be introduced along with expression constructs for immunomodulatory molecules, such as cytokines, which may increase the immune response or modulate the type of immune response produced in order to produce a response which will be more effective in eliminating the cancer.

The marker nucleic acid molecules can be inserted into vectors and used as gene therapy vectors. Gene therapy vectors can be delivered to a subject by, for example, intravenous injection, local administration (U.S. Patent 5,328,470), or by stereotactic injection (see, e.g., Chen et al., 1994, Proc. Natl. Acad. Sci. USA 91:3054-3057). The pharmaceutical preparation of the gene therapy vector can include the gene therapy vector in an acceptable diluent, or can comprise a slow release matrix in which the gene delivery vehicle is imbedded. Alternatively, where the complete gene delivery vector can be produced intact from recombinant cells, e.g. retroviral vectors, the pharmaceutical preparation can include one or more cells which produce the gene delivery system.

The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

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V. Predictive Medicine

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The present invention pertains to the field of predictive medicine in which diagnostic assays, prognostic assays, pharmacogenomics, and monitoring clinical trails are used for prognostic (predictive) purposes to thereby treat an individual prophylactically. Accordingly, one aspect of the present invention relates to diagnostic assays for determining the level of expression of one or more marker proteins or nucleic acids, in order to determine whether an individual is at risk of developing cervical cancer. Such assays can be used for prognostic or predictive purposes to thereby prophylactically treat an individual prior to the onset of the cancer.

Yet another aspect of the invention pertains to monitoring the influence of agents (e.g., drugs or other compounds administered either to inhibit cervical cancer or to treat or prevent any other disorder {i.e. in order to understand any cervical carcinogenic effects that such treatment may have}) on the expression or activity of a marker of the invention in clinical trials. These and other agents are described in further detail in the following sections.

A. Diagnostic Assays

An exemplary method for detecting the presence or absence of a marker protein or nucleic acid in a biological sample involves obtaining a biological sample (e.g. a cervical-associated body fluid) from a test subject and contacting the biological sample with a compound or an agent capable of detecting the polypeptide or nucleic acid (e.g., mRNA, genomic DNA, or cDNA). The detection methods of the invention can thus be used to detect mRNA, protein, cDNA, or genomic DNA, for example, in a biological sample in vitro as well as in vivo. For example, in vitro techniques for detection of mRNA include Northern hybridizations and in situ hybridizations. In vitro techniques for detection of a marker protein include enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations and immunofluorescence. In vitro techniques for detection of genomic DNA include Southern hybridizations. Furthermore, in vivo techniques for detection of a marker protein include introducing into a subject a labeled antibody directed against the protein or fragment thereof. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

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A general principle of such diagnostic and prognostic assays involves preparing a sample or reaction mixture that may contain a marker, and a probe, under appropriate conditions and for a time sufficient to allow the marker and probe to interact and bind, thus forming a complex that can be removed and/or detected in the reaction mixture. These assays can be conducted in a variety of ways.

For example, one method to conduct such an assay would involve anchoring the marker or probe onto a solid phase support, also referred to as a substrate, and detecting target marker/probe complexes anchored on the solid phase at the end of the reaction. In one embodiment of such a method, a sample from a subject, which is to be assayed for presence and/or concentration of marker, can be anchored onto a carrier or solid phase support. In another embodiment, the reverse situation is possible, in which the probe can be anchored to a solid phase and a sample from a subject can be allowed to react as an unanchored component of the assay.

There are many established methods for anchoring assay components to a solid phase. These include, without limitation, marker or probe molecules which are immobilized through conjugation of biotin and streptavidin. Such biotinylated assay components can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques known in the art (e.g., biotinylation kit, Pierce Chemicals, Rockford, IL), and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical). In certain embodiments, the surfaces with immobilized assay components can be prepared in advance and stored.

Other suitable carriers or solid phase supports for such assays include any material capable of binding the class of molecule to which the marker or probe belongs. Well-known supports or carriers include, but are not limited to, glass, polystyrene, nylon, polypropylene, nylon, polyethylene, dextran, amylases, natural and modified celluloses, polyacrylamides, gabbros, and magnetite.

In order to conduct assays with the above mentioned approaches, the non-immobilized component is added to the solid phase upon which the second component is anchored. After the reaction is complete, uncomplexed components may be removed (e.g., by washing) under conditions such that any complexes formed will remain immobilized upon the solid phase. The detection of marker/probe complexes anchored to the solid phase can be accomplished in a number of methods outlined herein.

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In a preferred embodiment, the probe, when it is the unanchored assay component, can be labeled for the purpose of detection and readout of the assay, either directly or indirectly, with detectable labels discussed herein and which are well-known to one skilled in the art.

It is also possible to directly detect marker/probe complex formation without further manipulation or labeling of either component (marker or probe), for example by utilizing the technique of fluorescence energy transfer (see, for example, Lakowicz et al., U.S. Patent No. 5,631,169; Stavrianopoulos, et al., U.S. Patent No. 4,868,103). A fluorophore label on the first, 'donor' molecule is selected such that, upon excitation with incident light of appropriate wavelength, its emitted fluorescent energy will be absorbed by a fluorescent label on a second 'acceptor' molecule, which in turn is able to fluoresce due to the absorbed energy. Alternately, the 'donor' protein molecule may simply utilize the natural fluorescent energy of tryptophan residues. Labels are chosen that emit different wavelengths of light, such that the 'acceptor' molecule label may be differentiated from that of the 'donor'. Since the efficiency of energy transfer between the labels is related to the distance separating the molecules, spatial relationships between the molecules can be assessed. In a situation in which binding occurs between the molecules, the fluorescent emission of the 'acceptor' molecule label in the assay should be maximal. An FET binding event can be conveniently measured through standard fluorometric detection means well known in the art (e.g., using a fluorimeter).

In another embodiment, determination of the ability of a probe to recognize a marker can be accomplished without labeling either assay component (probe or marker) by utilizing a technology such as real-time Biomolecular Interaction Analysis (BIA) (see, e.g., Sjolander, S. and Urbaniczky, C., 1991, Anal. Chem. 63:2338-2345 and Szabo et al., 1995, Curr. Opin. Struct. Biol. 5:699-705). As used herein, "BIA" or "surface plasmon resonance" is a technology for studying biospecific interactions in real time, without labeling any of the interactants (e.g., BIAcore). Changes in the mass at the binding surface (indicative of a binding event) result in alterations of the refractive index of light near the surface (the optical phenomenon of surface plasmon resonance (SPR)), resulting in a detectable signal which can be used as an indication of real-time reactions between biological molecules.

Alternatively, in another embodiment, analogous diagnostic and prognostic assays can be conducted with marker and probe as solutes in a liquid phase. In such an assay, the complexed marker and probe are separated from uncomplexed components by any of a number of standard techniques, including but not limited to: 5 differential centrifugation, chromatography, electrophoresis and immunoprecipitation. In differential centrifugation, marker/probe complexes may be separated from uncomplexed assay components through a series of centrifugal steps, due to the different sedimentation equilibria of complexes based on their different sizes and densities (see, for example, Rivas, G., and Minton, A.P., 1993, Trends Biochem Sci. 18(8):284-7). Standard chromatographic techniques may also be utilized to separate complexed molecules from uncomplexed ones. For example, gel filtration chromatography separates molecules based on size, and through the utilization of an appropriate gel filtration resin in a column format, for example, the relatively larger complex may be separated from the relatively smaller uncomplexed components. Similarly, the relatively 15 different charge properties of the marker/probe complex as compared to the uncomplexed components may be exploited to differentiate the complex from uncomplexed components, for example through the utilization of ion-exchange chromatography resins. Such resins and chromatographic techniques are well known to one skilled in the art (see, e.g., Heegaard, N.H., 1998, J. Mol. Recognit. Winter 11(1-6):141-8; Hage, D.S., and Tweed, S.A. J Chromatogr B Biomed Sci Appl 1997 Oct 20 10;699(1-2):499-525). Gel electrophoresis may also be employed to separate complexed assay components from unbound components (see, e.g., Ausubel et al., ed., Current Protocols in Molecular Biology, John Wiley & Sons, New York, 1987-1999). In this technique, protein or nucleic acid complexes are separated based on size or charge, for 25 example. In order to maintain the binding interaction during the electrophoretic process, non-denaturing gel matrix materials and conditions in the absence of reducing agent are typically preferred. Appropriate conditions to the particular assay and components thereof will be well known to one skilled in the art.

In a particular embodiment, the level of marker mRNA can be
determined both by *in situ* and by *in vitro* formats in a biological sample using methods
known in the art. The term "biological sample" is intended to include tissues, cells,
biological fluids and isolates thereof, isolated from a subject, as well as tissues, cells and
fluids present within a subject. Many expression detection methods use isolated RNA.

For *in vitro* methods, any RNA isolation technique that does not select against the isolation of mRNA can be utilized for the purification of RNA from cervical cells (see, *e.g.*, Ausubel *et al.*, ed., *Current Protocols in Molecular Biology*, John Wiley & Sons, New York 1987-1999). Additionally, large numbers of tissue samples can readily be processed using techniques well known to those of skill in the art, such as, for example, the single-step RNA isolation process of Chomczynski (1989, U.S. Patent No. 4,843,155).

The isolated mRNA can be used in hybridization or amplification assays that include, but are not limited to, Southern or Northern analyses, polymerase chain reaction analyses and probe arrays. One preferred diagnostic method for the detection of mRNA levels involves contacting the isolated mRNA with a nucleic acid molecule (probe) that can hybridize to the mRNA encoded by the gene being detected. The nucleic acid probe can be, for example, a full-length cDNA, or a portion thereof, such as an oligonucleotide of at least 7, 15, 30, 50, 100, 250 or 500 nucleotides in length and sufficient to specifically hybridize under stringent conditions to a mRNA or genomic DNA encoding a marker of the present invention. Other suitable probes for use in the diagnostic assays of the invention are described herein. Hybridization of an mRNA with the probe indicates that the marker in question is being expressed.

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In one format, the mRNA is immobilized on a solid surface and contacted with a probe, for example by running the isolated mRNA on an agarose gel and transferring the mRNA from the gel to a membrane, such as nitrocellulose. In an alternative format, the probe(s) are immobilized on a solid surface and the mRNA is contacted with the probe(s), for example, in an Affymetrix gene chip array. A skilled artisan can readily adapt known mRNA detection methods for use in detecting the level of mRNA encoded by the markers of the present invention.

An alternative method for determining the level of mRNA marker in a sample involves the process of nucleic acid amplification, e.g., by rtPCR (the experimental embodiment set forth in Mullis, 1987, U.S. Patent No. 4,683,202), ligase chain reaction (Barany, 1991, Proc. Natl. Acad. Sci. USA, 88:189-193), self sustained sequence replication (Guatelli et al., 1990, Proc. Natl. Acad. Sci. USA 87:1874-1878), transcriptional amplification system (Kwoh et al., 1989, Proc. Natl. Acad. Sci. USA 86:1173-1177), Q-Beta Replicase (Lizardi et al., 1988, Bio/Technology 6:1197), rolling circle replication (Lizardi et al., U.S. Patent No. 5,854,033) or any other nucleic acid

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amplification method, followed by the detection of the amplified molecules using techniques well known to those of skill in the art. These detection schemes are especially useful for the detection of nucleic acid molecules if such molecules are present in very low numbers. As used herein, amplification primers are defined as being a pair of nucleic acid molecules that can anneal to 5' or 3' regions of a gene (plus and minus strands, respectively, or vice-versa) and contain a short region in between. In general, amplification primers are from about 10 to 30 nucleotides in length and flank a region from about 50 to 200 nucleotides in length. Under appropriate conditions and with appropriate reagents, such primers permit the amplification of a nucleic acid molecule comprising the nucleotide sequence flanked by the primers.

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For *in situ* methods, mRNA does not need to be isolated from the cervical cells prior to detection. In such methods, a cell or tissue sample is prepared/processed using known histological methods. The sample is then immobilized on a support, typically a glass slide, and then contacted with a probe that can hybridize to mRNA that encodes the marker.

As an alternative to making determinations based on the absolute expression level of the marker, determinations may be based on the normalized expression level of the marker. Expression levels are normalized by correcting the absolute expression level of a marker by comparing its expression to the expression of a gene that is not a marker, *e.g.*, a housekeeping gene that is constitutively expressed. Suitable genes for normalization include housekeeping genes such as the actin gene, or epithelial cell-specific genes. This normalization allows the comparison of the expression level in one sample, *e.g.*, a patient sample, to another sample, *e.g.*, a noncervical cancer sample, or between samples from different sources.

Alternatively, the expression level can be provided as a relative expression level. To determine a relative expression level of a marker, the level of expression of the marker is determined for 10 or more samples of normal versus cancer cell isolates, preferably 50 or more samples, prior to the determination of the expression level for the sample in question. The mean expression level of each of the genes assayed in the larger number of samples is determined and this is used as a baseline expression level for the marker. The expression level of the marker determined for the test sample (absolute level of expression) is then divided by the mean expression value obtained for that marker. This provides a relative expression level.

Preferably, the samples used in the baseline determination will be from cervical cancer or from non-cervical cancer cells of cervical tissue. The choice of the cell source is dependent on the use of the relative expression level. Using expression found in normal tissues as a mean expression score aids in validating whether the marker assayed is cervical specific (versus normal cells). In addition, as more data is accumulated, the mean expression value can be revised, providing improved relative expression values based on accumulated data. Expression data from cervical cells provides a means for grading the severity of the cervical cancer state.

In another embodiment of the present invention, a marker protein is

detected. A preferred agent for detecting marker protein of the invention is an antibody capable of binding to such a protein or a fragment thereof, preferably an antibody with a detectable label. Antibodies can be polyclonal, or more preferably, monoclonal. An intact antibody, or a fragment or derivative thereof (e.g., Fab or F(ab')₂) can be used.

The term "labeled", with regard to the probe or antibody, is intended to encompass direct labeling of the probe or antibody by coupling (i.e., physically linking) a detectable substance to the probe or antibody, as well as indirect labeling of the probe or antibody by reactivity with another reagent that is directly labeled. Examples of indirect labeling include detection of a primary antibody using a fluorescently labeled secondary antibody and end-labeling of a DNA probe with biotin such that it can be detected with

fluorescently labeled streptavidin.

Proteins from cervical cells can be isolated using techniques that are well known to those of skill in the art. The protein isolation methods employed can, for example, be such as those described in Harlow and Lane (Harlow and Lane, 1988, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York).

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A variety of formats can be employed to determine whether a sample contains a protein that binds to a given antibody. Examples of such formats include, but are not limited to, enzyme immunoassay (EIA), radioimmunoassay (RIA), Western blot analysis and enzyme linked immunoabsorbant assay (ELISA). A skilled artisan can readily adapt known protein/antibody detection methods for use in determining whether cervical cells express a marker of the present invention.

In one format, antibodies, or antibody fragments or derivatives, can be used in methods such as Western blots or immunofluorescence techniques to detect the expressed proteins. In such uses, it is generally preferable to immobilize either the antibody or proteins on a solid support. Suitable solid phase supports or carriers include any support capable of binding an antigen or an antibody. Well-known supports or carriers include glass, polystyrene, polypropylene, polyethylene, dextran, nylon, amylases, natural and modified celluloses, polyacrylamides, gabbros, and magnetite.

One skilled in the art will know many other suitable carriers for binding antibody or antigen, and will be able to adapt such support for use with the present invention. For example, protein isolated from cervical cells can be run on a polyacrylamide gel electrophoresis and immobilized onto a solid phase support such as nitrocellulose. The support can then be washed with suitable buffers followed by treatment with the detectably labeled antibody. The solid phase support can then be washed with the buffer a second time to remove unbound antibody. The amount of bound label on the solid support can then be detected by conventional means.

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The invention also encompasses kits for detecting the presence of a marker protein or nucleic acid in a biological sample (e.g., cervical smear). Such kits can be used to determine if a subject is suffering from or is at increased risk of developing cervical cancer. For example, the kit can comprise a labeled compound or agent capable of detecting a marker protein or nucleic acid in a biological sample and means for determining the amount of the protein or mRNA in the sample (e.g., an antibody which binds the protein or a fragment thereof, or an oligonucleotide probe which binds to DNA or mRNA encoding the protein). Kits can also include instructions for interpreting the results obtained using the kit.

For antibody-based kits, the kit can comprise, for example: (1) a first antibody (e.g., attached to a solid support) which binds to a marker protein; and, optionally, (2) a second, different antibody which binds to either the protein or the first antibody and is conjugated to a detectable label.

For oligonucleotide-based kits, the kit can comprise, for example: (1) an oligonucleotide, e.g., a detectably labeled oligonucleotide, which hybridizes to a nucleic acid sequence encoding a marker protein or (2) a pair of primers useful for amplifying a marker nucleic acid molecule. The kit can also comprise, e.g., a buffering agent, a preservative, or a protein stabilizing agent. The kit can further comprise components

necessary for detecting the detectable label (e.g., an enzyme or a substrate). The kit can also contain a control sample or a series of control samples which can be assayed and compared to the test sample. Each component of the kit can be enclosed within an individual container and all of the various containers can be within a single package, along with instructions for interpreting the results of the assays performed using the kit.

B. Pharmacogenomics

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The markers of the invention are also useful as pharmacogenomic markers. As used herein, a "pharmacogenomic marker" is an objective biochemical marker whose expression level correlates with a specific clinical drug response or susceptibility in a patient (see, e.g., McLeod et al. (1999) Eur. J. Cancer 35(12): 1650-1652). The presence or quantity of the pharmacogenomic marker expression is related to the predicted response of the patient and more particularly the patient's tumor to therapy with a specific drug or class of drugs. By assessing the presence or quantity of the expression of one or more pharmacogenomic markers in a patient, a drug therapy which is most appropriate for the patient, or which is predicted to have a greater degree of success, may be selected. For example, based on the presence or quantity of RNA or protein encoded by specific tumor markers in a patient, a drug or course of treatment may be selected that is optimized for the treatment of the specific tumor likely to be present in the patient. The use of pharmacogenomic markers therefore permits selecting or designing the most appropriate treatment for each cancer patient without trying different drugs or regimes.

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Another aspect of pharmacogenomics deals with genetic conditions that alters the way the body acts on drugs. These pharmacogenetic conditions can occur either as rare defects or as polymorphisms. For example, glucose-6-phosphate dehydrogenase (G6PD) deficiency is a common inherited enzymopathy in which the main clinical complication is hemolysis after ingestion of oxidant drugs (anti-malarials, sulfonamides, analgesics, nitrofurans) and consumption of fava beans.

As an illustrative embodiment, the activity of drug metabolizing enzymes is a major determinant of both the intensity and duration of drug action. The discovery of genetic polymorphisms of drug metabolizing enzymes (e.g., N-acetyltransferase 2 (NAT 2) and cytochrome P450 enzymes CYP2D6 and CYP2C19) has provided an explanation as to why some patients do not obtain the expected drug effects or show

exaggerated drug response and serious toxicity after taking the standard and safe dose of a drug. These polymorphisms are expressed in two phenotypes in the population, the extensive metabolizer (EM) and poor metabolizer (PM). The prevalence of PM is different among different populations. For example, the gene coding for CYP2D6 is highly polymorphic and several mutations have been identified in PM, which all lead to the absence of functional CYP2D6. Poor metabolizers of CYP2D6 and CYP2C19 quite frequently experience exaggerated drug response and side effects when they receive standard doses. If a metabolite is the active therapeutic moiety, a PM will show no therapeutic response, as demonstrated for the analgesic effect of codeine mediated by its CYP2D6-formed metabolite morphine. The other extreme are the so called ultra-rapid metabolizers who do not respond to standard doses. Recently, the molecular basis of ultra-rapid metabolism has been identified to be due to CYP2D6 gene amplification.

Thus, the level of expression of a marker of the invention in an individual can be determined to thereby select appropriate agent(s) for therapeutic or prophylactic treatment of the individual. In addition, pharmacogenetic studies can be used to apply genotyping of polymorphic alleles encoding drug-metabolizing enzymes to the identification of an individual's drug responsiveness phenotype. This knowledge, when applied to dosing or drug selection, can avoid adverse reactions or therapeutic failure and thus enhance therapeutic or prophylactic efficiency when treating a subject with a modulator of expression of a marker of the invention.

C. Monitoring Clinical Trials

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Monitoring the influence of agents (e.g., drug compounds) on the level of expression of a marker of the invention can be applied not only in basic drug screening, but also in clinical trials. For example, the effectiveness of an agent to affect marker expression can be monitored in clinical trials of subjects receiving treatment for cervical cancer. In a preferred embodiment, the present invention provides a method for monitoring the effectiveness of treatment of a subject with an agent (e.g., an agonist, antagonist, peptidomimetic, protein, peptide, nucleic acid, small molecule, or other drug candidate) comprising the steps of (i) obtaining a pre-administration sample from a subject prior to administration of the agent; (ii) detecting the level of expression of one or more selected markers of the invention in the pre-administration sample; (iii) obtaining one or more post-administration samples from the subject; (iy) detecting the

level of expression of the marker(s) in the post-administration samples; (v) comparing the level of expression of the marker(s) in the pre-administration sample with the level of expression of the marker(s) in the post-administration sample or samples; and (vi) altering the administration of the agent to the subject accordingly. For example, increased expression of the marker gene(s) during the course of treatment may indicate ineffective dosage and the desirability of increasing the dosage. Conversely, decreased expression of the marker gene(s) may indicate efficacious treatment and no need to change dosage.

D. Electronic Apparatus Readable Media and Arrays

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Electronic apparatus readable media comprising a marker of the present invention is also provided. As used herein, "electronic apparatus readable media" refers to any suitable medium for storing, holding or containing data or information that can be read and accessed directly by an electronic apparatus. Such media can include, but are not limited to: magnetic storage media, such as floppy discs, hard disc storage medium, and magnetic tape; optical storage media such as compact disc; electronic storage media such as RAM, ROM, EPROM, EEPROM and the like; general hard disks and hybrids of these categories such as magnetic/optical storage media. The medium is adapted or configured for having recorded thereon a marker of the present invention.

As used herein, the term "electronic apparatus" is intended to include any suitable computing or processing apparatus or other device configured or adapted for storing data or information. Examples of electronic apparatus suitable for use with the present invention include stand-alone computing apparatus; networks, including a local area network (LAN), a wide area network (WAN) Internet, Intranet, and Extranet; electronic appliances such as a personal digital assistants (PDAs), cellular phone, pager and the like; and local and distributed processing systems.

As used herein, "recorded" refers to a process for storing or encoding information on the electronic apparatus readable medium. Those skilled in the art can readily adopt any of the presently known methods for recording information on known media to generate manufactures comprising the markers of the present invention.

A variety of software programs and formats can be used to store the marker information of the present invention on the electronic apparatus readable medium. For example, the marker nucleic acid sequence can be represented in a word

processing text file, formatted in commercially-available software such as WordPerfect and MicroSoft Word, or represented in the form of an ASCII file, stored in a database application, such as DB2, Sybase, Oracle, or the like, as well as in other forms. Any number of data processor structuring formats (*e.g.*, text file or database) may be employed in order to obtain or create a medium having recorded thereon the markers of the present invention.

By providing the markers of the invention in readable form, one can routinely access the marker sequence information for a variety of purposes. For example, one skilled in the art can use the nucleotide or amino acid sequences of the present invention in readable form to compare a target sequence or target structural motif with the sequence information stored within the data storage means. Search means are used to identify fragments or regions of the sequences of the invention which match a particular target sequence or target motif.

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The present invention therefore provides a medium for holding instructions for performing a method for determining whether a subject has cervical cancer or a pre-disposition to cervical cancer, wherein the method comprises the steps of determining the presence or absence of a marker and based on the presence or absence of the marker, determining whether the subject has cervical cancer or a pre-disposition to cervical cancer and/or recommending a particular treatment for cervical cancer or pre-cervical cancer condition.

The present invention further provides in an electronic system and/or in a network, a method for determining whether a subject has cervical cancer or a pre-disposition to cervical cancer associated with a marker wherein the method comprises the steps of determining the presence or absence of the marker, and based on the presence or absence of the marker, determining whether the subject has cervical cancer or a pre-disposition to cervical cancer, and/or recommending a particular treatment for the cervical cancer or pre-cervical cancer condition. The method may further comprise the step of receiving phenotypic information associated with the subject and/or acquiring from a network phenotypic information associated with the subject.

The present invention also provides in a network, a method for determining whether a subject has cervical cancer or a pre-disposition to cervical cancer associated with a marker, said method comprising the steps of receiving information associated with the marker receiving phenotypic information associated with the subject,

acquiring information from the network corresponding to the marker and/or cervical cancer, and based on one or more of the phenotypic information, the marker, and the acquired information, determining whether the subject has a cervical cancer or a pre-disposition to cervical cancer. The method may further comprise the step of recommending a particular treatment for the cervical cancer or pre-cervical cancer condition.

The present invention also provides a business method for determining whether a subject has cervical cancer or a pre-disposition to cervical cancer, said method comprising the steps of receiving information associated with the marker, receiving phenotypic information associated with the subject, acquiring information from the network corresponding to the marker and/or cervical cancer, and based on one or more of the phenotypic information, the marker, and the acquired information, determining whether the subject has cervical cancer or a pre-disposition to cervical cancer. The method may further comprise the step of recommending a particular treatment for the cervical cancer or pre-cervical cancer condition.

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The invention also includes an array comprising a marker of the present invention. The array can be used to assay expression of one or more genes in the array. In one embodiment, the array can be used to assay gene expression in a tissue to ascertain tissue specificity of genes in the array. In this manner, up to about 7600 genes can be simultaneously assayed for expression. This allows a profile to be developed showing a battery of genes specifically expressed in one or more tissues.

In addition to such qualitative determination, the invention allows the quantitation of gene expression. Thus, not only tissue specificity, but also the level of expression of a battery of genes in the tissue is ascertainable. Thus, genes can be grouped on the basis of their tissue expression *per se* and level of expression in that tissue. This is useful, for example, in ascertaining the relationship of gene expression between or among tissues. Thus, one tissue can be perturbed and the effect on gene expression in a second tissue can be determined. In this context, the effect of one cell type on another cell type in response to a biological stimulus can be determined. Such a determination is useful, for example, to know the effect of cell-cell interaction at the level of gene expression. If an agent is administered therapeutically to treat one cell type but has an undesirable effect on another cell type, the invention provides an assay to determine the molecular basis of the undesirable effect and thus provides the

opportunity to co-administer a counteracting agent or otherwise treat the undesired effect. Similarly, even within a single cell type, undesirable biological effects can be determined at the molecular level. Thus, the effects of an agent on expression of other than the target gene can be ascertained and counteracted.

In another embodiment, the array can be used to monitor the time course of expression of one or more genes in the array. This can occur in various biological contexts, as disclosed herein, for example development of cervical cancer, progression of cervical cancer, and processes, such a cellular transformation associated with cervical cancer.

The array is also useful for ascertaining the effect of the expression of a gene on the expression of other genes in the same cell or in different cells. This provides, for example, for a selection of alternate molecular targets for therapeutic intervention if the ultimate or downstream target cannot be regulated.

The array is also useful for ascertaining differential expression patterns of one or more genes in normal and abnormal cells. This provides a battery of genes that could serve as a molecular target for diagnosis or therapeutic intervention.

E. Surrogate Markers

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The markers of the invention may serve as surrogate markers for one or more disorders or disease states or for conditions leading up to disease states, and in particular, cervical cancer. As used herein, a "surrogate marker" is an objective biochemical marker which correlates with the absence or presence of a disease or disorder, or with the progression of a disease or disorder (e.g., with the presence or absence of a tumor). The presence or quantity of such markers is independent of the disease. Therefore, these markers may serve to indicate whether a particular course of treatment is effective in lessening a disease state or disorder. Surrogate markers are of particular use when the presence or extent of a disease state or disorder is difficult to assess through standard methodologies (e.g., early stage tumors), or when an assessment of disease progression is desired before a potentially dangerous clinical endpoint is reached (e.g., an assessment of cardiovascular disease may be made using cholesterol levels as a surrogate marker, and an analysis of HIV infection may be made using HIV RNA levels as a surrogate marker, well in advance of the undesirable clinical outcomes of myocardial infarction or fully-developed AIDS). Examples of the use of surrogate

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markers in the art include: Koomen et al. (2000) J. Mass. Spectrom. 35: 258-264; and James (1994) AIDS Treatment News Archive 209.

The markers of the invention are also useful as pharmacodynamic markers. As used herein, a "pharmacodynamic marker" is an objective biochemical marker which correlates specifically with drug effects. The presence or quantity of a pharmacodynamic marker is not related to the disease state or disorder for which the drug is being administered; therefore, the presence or quantity of the marker is indicative of the presence or activity of the drug in a subject. For example, a pharmacodynamic marker may be indicative of the concentration of the drug in a biological tissue, in that the marker is either expressed or transcribed or not expressed or transcribed in that tissue in relationship to the level of the drug. In this fashion, the distribution or uptake of the drug may be monitored by the pharmacodynamic marker. Similarly, the presence or quantity of the pharmacodynamic marker may be related to the presence or quantity of the metabolic product of a drug, such that the presence or quantity of the marker is indicative of the relative breakdown rate of the drug in vivo. Pharmacodynamic markers are of particular use in increasing the sensitivity of detection of drug effects, particularly when the drug is administered in low doses. Since even a small amount of a drug may be sufficient to activate multiple rounds of marker transcription or expression, the amplified marker may be in a quantity which is more readily detectable than the drug itself. Also, the marker may be more easily detected due to the nature of the marker itself; for example, using the methods described herein, antibodies may be employed in an immune-based detection system for a protein marker, or marker-specific radiolabeled probes may be used to detect a mRNA marker. Furthermore, the use of a pharmacodynamic marker may offer mechanism-based prediction of risk due to drug treatment beyond the range of possible direct observations. Examples of the use of pharmacodynamic markers in the art include: Matsuda et al. US 6,033,862; Hattis et al. (1991) Env. Health Perspect. 90: 229-238; Schentag (1999) Am. J. Health-Syst. Pharm. 56 Suppl. 3: S21-S24; and Nicolau (1999) Am, J. Health-Syst. Pharm. 56 Suppl. 3: S16-S20.

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VI. Experimental Protocol

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A. Identification of clones

Cervical tumor specific cDNA clones were identified by transcription profiling using mRNA from 12 cervical tumors, 5 CIN III, 5 CIN I and 12 normal cervical tissues. The subtracted libraries were constructed using mRNA from at least three independent normal ectocervix, B-lymphocytes, T-lymphocytes and other white blood cells (in activated and resting states) as drivers and four independent stage 1B cervical tumors or four independent C1N III cervical samples as testers. The top upregulated clones in tumors or C1N III cervical tissues, as determined by proprietary statistical analysis methods, were selected. The clusters in which the selected clones belong were blasted against both public and proprietary sequence databases in order to identify other EST sequences or clusters with significant overlap. Thus, contiguous EST sequences and/or clusters were assembled into full-length genes.

An identification of protein sequence corresponding to the clone was accomplished by obtaining one of the following:

- a) a direct match between the protein sequence and at least one EST sequence in one of its 6 possible translations;
- b) a direct match between the nucleotide sequence for the mRNA corresponding to the protein sequence and at least one EST sequence;
- c) a match between the protein sequence and a contiguous assembly (contig) of the EST sequences with other available EST sequences in the databases in one of its 6 possible translations; or
- d) a match between the nucleotide sequence for the mRNA corresponding to the protein sequence and a contiguous assembly of the EST sequences with other available EST sequences in the databases in one of its 6 possible translations.

VII. Summary of the Data

Tables 1-3 list the markers obtained using the foregoing protocol. The tables provide the name of the gene corresponding to the marker ("Gene Name"), the sequence listing identifier of the cDNA sequence of a nucleotide transcript encoded by or corresponding to the marker ("SEQ ID NO (nts)"), the sequence listing identifier of the amino acid sequence of a protein encoded by the nucleotide transcript ("SEQ ID NO

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(AAs)"), and the location of the protein coding sequence within the cDNA sequence ("CDS").

Table 1 lists all of the markers of the invention which are over-expressed in cervical cancer cells compared to normal (*i.e.*, non-cancerous) cervical cells. Table 2 lists newly-identified nucleotide and amino acid sequences useful as cervical cancer markers. Table 3 lists newly-identified nucleotide sequences useful as cervical cancer markers.

Other Embodiments

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Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims:

What is claimed:

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- 1. An isolated nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1, 3, 5, 7, 143, 145, 147, 149, 151, 167, 203, 217, 231, 233, 51, 65, 67, 68, 100, and 153.
 - 2. A vector which contains the nucleic acid molecule of claim 1.
 - 3. A host cell which contains the nucleic acid molecule of claim 1.

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- 4. A method of assessing whether a patient is afflicted with cervical cancer, the method comprising comparing:
 - a) the level of expression of a marker in a patient sample, wherein the marker is selected from Table 1; and
 - b) the normal level of expression of the marker in a control non-cervical cancer sample,

wherein a significant increase in the level of expression of the marker in the patient sample and the normal level is an indication that the patient is afflicted with cervical cancer.

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- 5. An isolated polypeptide which is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1, 3, 5, 7, 143, 145, 147, 149, 151, 167, 203, 217, 231, and 233.
 - 6. An antibody which selectively binds to the polypeptide of claim 5.
- 7. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 4, 6, 8, 144, 146, 148, 150, 152, 168, 204, 218, 232, and 234.

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8. An antibody which selectively binds to the polypeptide of claim 7.

SEQUENCE LISTING

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<110> Millennium Pharmaceuticals, Inc. et al.
<120> NOVEL GENES, COMPOSITIONS, KITS, AND METHODS FOR
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accectcaac ceetgtttte ceetgeette ettgeagagg ceatggagga egaggagaga 240
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Gln 865	Glu	Glu	Tyr	Ala	Cys 870	Leu	Leu	Lys	Val	Lys 875	Asp	Asp	Leu	Glu	Asp 880

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Ser Lys Asn Lys Gln Glu Leu Glu Tyr Lys Ser Lys Leu Lys Ala Leu 885 890 Asn Glu Glu Leu His Leu Gln Arg Ile Asn Pro Thr Thr Val Lys Met 900 905 Lys Ser Ser Val Phe Asp Glu Asp Lys Thr Phe Val Ala Glu Thr Leu 920 Glu Met Gly Glu Val Val Glu Lys Asp Thr Thr Glu Leu Met Glu Lys 935 Leu Glu Val Thr Lys Arg Glu Lys Leu Glu Leu Ser Gln Arg Leu Ser 950 955 Asp Leu Ser Glu Gln Leu Lys Gln Lys His Gly Glu Ile Ser Phe Leu 965 970 Asn Glu Glu Val Lys Ser Leu Lys Gln Glu Lys Glu Gln Val Ser Leu 980 985 Arg Cys Arg Glu Leu Glu Ile Ile Ile Asn His Asn Arg Ala Glu Asn 995 1000 1005 Val Gln Ser Cys Asp Thr Gln Val Ser Ser Leu Leu Asp Gly Val Val 1010 1015 1020 Thr Met Thr Ser Arg Gly Ala Glu Gly Ser Val Ser Lys Val Asn Lys 1025 1030 1035 1040 Ser Phe Gly Glu Glu Ser Lys Ile Met Val Glu Asp Lys Val Ser Phe 1045 1050 1055 Glu Asn Met Thr Val Gly Glu Glu Ser Lys Gln Glu Gln Leu Ile Leu 1060 1065 1070 Asp His Leu Pro Ser Val Thr Lys Glu Ser Ser Leu Arg Ala Thr Gln 1,075 1080 1085 Pro Ser Glu Asn Asp Lys Leu Gln Lys Glu Leu Asn Val Leu Lys Ser 1090 1095 1100 Glu Gln Asn Asp Leu Arg Leu Gln Met Glu Ala Gln Arg Ile Cys Leu 1105 1110 1115 1120 Ser Leu Val Tyr Ser Thr His Val Asp Gln Val Arg Glu Tyr Met Glu 1125 1130 1135 Asn Glu Lys Asp Lys Ala Leu Cys Ser Leu Lys Glu Glu Leu Ile Phe 1140 1145 1150 Ala Gln Glu Glu Lys Ile Lys Glu Leu Gln Lys Ile His Gln Leu Glu 1155 1160 1165 Leu Gln Thr Met Lys Thr Gln Glu Thr Gly Asp Glu Gly Lys Pro Leu 1170 1175 1180 His Leu Leu Ile Gly Lys Leu Gln Lys Ala Val Ser Glu Glu Cys Ser 1185 1190 1195 Tyr Phe Leu Gln Thr Leu Cys Ser Val Leu Gly Glu Tyr Tyr Thr Pro 1205 1210 Ala Leu Lys Cys Glu Val Asn Ala Glu Asp Lys Glu Asn Ser Gly Asp 1220 1225 Tyr Ile Ser Glu Asn Glu Asp Pro Glu Leu Gln Asp Tyr Arg Tyr Glu 1235 1240 1245 Val Gln Asp Phe Gln Glu Asn Met His Thr Leu Leu Asn Lys Val Thr 1255 Glu Glu Tyr Asn Lys Leu Leu Val Leu Gln Thr Arg Leu Ser Lys Ile 1270 1275 Trp Gly Gln Gln Thr Asp Gly Met Lys Leu Glu Phe Gly Glu Glu Asn 1285 1290 1295 Leu Pro Lys Glu Glu Thr Glu Phe Leu Ser Ile His Ser Gln Met Thr 1300 1305 1310 Asn Leu Glu Asp Ile Asp Val Asn His Lys Ser Lys Leu Ser Ser Leu 1315 1320 1325 Gln Asp Leu Glu Lys Thr Lys Leu Glu Glu Gln Val Gln Glu Leu Glu 1330 1335 1340 Ser Leu Ile Ser Ser Leu Gln Gln Gln Leu Lys Glu Thr Glu Gln Asn

1350 1345 1355 Tyr Glu Ala Glu Ile His Cys Leu Gln Lys Arg Leu Gln Ala Val Ser 1365 1370 1375 Glu Ser Thr Val Pro Pro Ser Leu Pro Val Asp Ser Val Val Ile Thr 1380 1385 Glu Ser Asp Ala Gln Arg Thr Met Tyr Pro Gly Ser Cys Val Lys 1395 1400 Asn Ile Asp Gly Thr Ile Glu Phe Ser Gly Glu Phe Gly Val Lys Glu 1410 1415 1420 Glu Thr Asn Ile Val Lys Leu Leu Glu Lys Gln Tyr Gln Glu Gln Leu 1430 1435 Glu Glu Val Ala Lys Val Ile Val Ser Met Ser Ile Ala Phe Ala 1445 1450 1455 Gln Gln Thr Glu Leu Ser Arg Ile Ser Gly Gly Lys Glu Asn Thr Ala 1460 1465 Ser Ser Lys Gln Ala His Ala Val Cys Gln Gln Glu Gln His Tyr Phe 1475 1480 Asn Glu Met Lys Leu Ser Gln Asp Gln Ile Gly Phe Gln Thr Phe Glu 1490 1495 1500 Thr Val Asp Val Lys Phe Lys Glu Glu Phe Lys Pro Leu Ser Lys Glu 1505 1510 1515 1520 Leu Gly Glu His Gly Lys Glu Ile Leu Leu Ser Asn Ser Asp Pro His 1525 1530 1535 Asp Ile Pro Glu Ser Lys Asp Cys Val Leu Thr Ile Ser Glu Glu Met 1540 1545 1550 Phe Ser Lys Asp Lys Thr Phe Ile Val Arg Gln Ser Ile His Asp Glu 1555 1560 1565 Ile Ser Val Ser Ser Met Asp Ala Ser Arg Gln Leu Met Leu Asn Glu 1570 1575 1580 Glu Gln Leu Glu Asp Met Arg Gln Glu Leu Val Arg Gln Tyr Gln Glu 1585 1590 1595 1600 His Gln Gln Ala Thr Glu Leu Leu Arg Gln Ala His Met Arg Gln Met 1605 1610 1615 Glu Arg Gln Arg Glu Asp Gln Glu Gln Leu Gln Glu Glu Ile Lys Arg 1620 1625 1630 Leu Asn Arg Gln Leu Ala Gln Arg Ser Ser Ile Asp Asn Glu Asn Leu 1635 1640 1645 Val Ser Glu Arg Glu Arg Val Leu Leu Glu Glu Leu Glu Ala Leu Lys 1650 1655 1660 Gln Leu Ser Leu Ala Gly Arg Glu Lys Leu Cys Cys Glu Leu Arg Asn 1665 1670 1675 Ser Ser Thr Gln Thr Gln Asn Gly Asn Glu Asn Gln Gly Glu Val Glu 1685 1690 1695 Glu Gln Thr Phe Lys Glu Lys Glu Leu Asp Arg Lys Pro Glu Asp Val 1700 1705 1710 Pro Pro Glu Ile Leu Ser Asn Glu Arg Tyr Ala Leu Gln Lys Ala Asn 1715 1720 1725 Asn Arg Leu Leu Lys Ile Leu Leu Glu Val Val Lys Thr Thr Ala Ala 1730 1735 1740 Val Glu Glu Thr Ile Gly Arg His Val Leu Gly Ile Leu Asp Arg Ser 1745 1750 1755 1760 Ser Lys Ser Gln Ser Ser Ala Ser Leu Ile Trp Arg Ser Glu Ala Glu 1765 1770 1775 Ala Ser Val Lys Ser Cys Val His Glu Glu His Thr Arg Val Thr Asp 1780 1785 1790 Glu Ser Ile Pro Ser Tyr Ser Gly Ser Asp Met Pro Arg Asn Asp Ile 1795 1800 1805 Asn Met Trp Ser Lys Val Thr Glu Glu Gly Thr Glu Leu Ser Gln Arg 1810 1815 1820

Leu Val Arg Ser Gly Phe Ala Gly Thr Glu Ile Asp Pro Glu Asn Glu 1825 1830 1835 1840 Glu Leu Met Leu Asn Ile Ser Ser Arg Leu Gln Ala Ala Val Glu Lys 1845 1850 Leu Leu Glu Ala Ile Ser Glu Thr Ser Ser Gln Leu Glu His Ala Lys 1860 - 1865 1870 Val Thr Gln Thr Glu Leu Met Arg Glu Ser Phe Arg Gln Lys Gln Glu 1875 1880 1885 Ala Thr Glu Ser Leu Lys Cys Gln Glu Glu Leu Arg Glu Arg Leu His 1890 1895 1900 Glu Glu Ser Arg Ala Arg Glu Gln Leu Ala Val Glu Leu Ser Lys Ala 1905 1910 1915 1920 Glu Gly Val Ile Asp Gly Tyr Ala Asp Glu Lys Thr Leu Phe Glu Arg 1925 1930 1935 Gln Ile Gln Glu Lys Thr Asp Ile Ile Asp Arg Leu Glu Gln Glu Leu 1940 1945 1950 Leu Cys Ala Ser Asn Arg Leu Gln Glu Leu Glu Ala Glu Gln Gln 1955 1960 1965 Ile Gln Glu Glu Arg Glu Leu Leu Ser Arg Gln Lys Glu Ala Met Lys 1970 1975 1980 Ala Glu Ala Gly Pro Val Glu Gln Gln Leu Leu Gln Glu Thr Glu Lys 1985 1990 1995 2000 Leu Met Lys Glu Lys Leu Glu Val Gln Cys Gln Ala Glu Lys Val Arg 2005 2010 2015 Asp Asp Leu Gln Lys Gln Val Lys Ala Leu Glu Ile Asp Val Glu Glu 2020 2025 2030 Gln Val Ser Arg Phe Ile Glu Leu Glu Gln Glu Lys Asn Thr Glu Leu 2035 2040 2045 Met Asp Leu Arg Gln Gln Asn Gln Ala Leu Glu Lys Gln Leu Glu Lys 2050 2055 2060 Met Arg Lys Phe Leu Asp Glu Gln Ala Ile Asp Arg Glu His Glu Arg 2065 2070 2075 2080 Asp Val Phe Gln Gln Glu Ile Gln Lys Leu Glu Gln Gln Leu Lys Val 2085 2090 2095 Val Pro Arg Phe Gln Pro Ile Ser Glu His Gln Thr Arg Glu Val Glu 2100 2105 2110 Gln Leu Ala Asn His Leu Lys Glu Lys Thr Asp Lys Cys Ser Glu Leu 2115 2120 2125 Leu Leu Ser Lys Glu Gln Leu Gln Arg Asp Ile Gln Glu Arg Asn Glu 2130 2135 2140 Glu Ile Glu Lys Leu Glu Phe Arg Val Arg Glu Leu Glu Gln Ala Leu 2145 2150 2155 2160 Leu Val Ser Ala Asp Thr Phe Gln Lys Val Glu Asp Arg Lys His Phe 2165 2170 2175 Gly Ala Val Glu Ala Lys Pro Glu Leu Ser Leu Glu Val Gln Leu Gln 2180 2185 2190 Ala Glu Arg Asp Ala Ile Asp Arg Lys Glu Lys Glu Ile Thr Asn Leu 2195 2200 2205 Glu Glu Gln Leu Glu Gln Phe Arg Glu Glu Leu Glu Asn Lys Asn Glu 2210 2215 2220 Glu Val Gln Gln Leu His Met Gln Leu Glu Ile Gln Lys Lys Glu Ser 2230 2235 Thr Thr Arg Leu Gln Glu Leu Glu Gln Glu Asn Lys Leu Phe Lys Asp 2245 2250 2255 Asp Met Glu Lys Leu Gly Leu Ala Ile Lys Glu Ser Asp Ala Met Ser 2260 2265 2270 Thr Gln Asp Gln His Val Leu Phe Gly Lys Phe Ala Gln Ile Ile Gln 2280 2285 Glu Lys Glu Val Glu Ile Asp Gln Leu Asn Glu Gln Val Thr Lys Leu

2295 2290 2300 Gln Gln Leu Lys Ile Thr Thr Asp Asn Lys Val Ile Glu Glu Lys 2315 2320 2310 Asn Glu Leu Ile Arg Asp Leu Glu Thr Gln Ile Glu Cys Leu Met Ser 2325 2330 Asp Gln Glu Cys Val Lys Arg Asn Arg Glu Glu Glu Ile Glu Gln Leu 2340 2345 Asn Glu Val Ile Glu Lys Leu Gln Gln Glu Leu Ala Asn Ile Gly Gln 2355 2360 Lys Thr Ser Met Asn Ala His Ser Leu Ser Glu Glu Ala Asp Ser Leu 2370 2375 2380 Lys His Gln Leu Asp Val Val Ile Ala Glu Lys Leu Ala Leu Glu Gln 2385 2390 2395 2400 Gln Val Glu Thr Ala Asn Glu Glu Met Thr Phe Met Lys Asn Val Leu 2405 2410 2415 Lys Glu Thr Asn Phe Lys Met Asn Gln Leu Thr Gln Glu Leu Phe Ser 2420 2425 2430 Leu Lys Arg Glu Arg Glu Ser Val Glu Lys Ile Gln Ser Ile Pro Glu 2435 2440 2445 Asn Ser Val Asn Val Ala Ile Asp His Leu Ser Lys Asp Lys Pro Glu 2450 2455 2460 Leu Glu Val Val Leu Thr Glu Asp Ala Leu Lys Ser Leu Glu Asn Gln 2465 2470 2475 2480 Thr Tyr Phe Lys Ser Phe Glu Glu Asn Gly Lys Gly Ser Ile Ile Asn 2485 2490 2495 Leu Glu Thr Arg Leu Leu Gln Leu Glu Ser Thr Val Ser Ala Lys Asp 2500 2505 2510 Leu Glu Leu Thr Gln Cys Tyr Lys Gln Ile Lys Asp Met Gln Glu Gln 2515 2520 2525 Gly Gln Phe Glu Thr Glu Met Leu Gln Lys Lys Ile Val Asn Leu Gln 2530 2535 2540 Lys Ile Val Glu Glu Lys Val Ala Ala Leu Val Ser Gln Ile Gln 2545 2550 2555 Leu Glu Ala Val Gln Glu Tyr Ala Lys Phe Cys Gln Asp Asn Gln Thr 2565 2570 Ile Ser Ser Glu Pro Glu Arq Thr Asn Ile Gln Asn Leu Asn Gln Leu 2580 2585 2590 Arg Glu Asp Glu Leu Gly Ser Asp Ile Ser Ala Leu Thr Leu Arg Ile 2595 2600 2605 Ser Glu Leu Glu Ser Gln Val Val Glu Met His Thr Ser Leu Ile Leu 2610 2615 2620 Glu Lys Glu Gln Val Glu Ile Ala Glu Lys Asn Val Leu Glu Lys Glu 2625 2630 2635 2640 Lys Lys Leu Glu Glu Lys Leu Glu Glu Gly Asn Glu Lys Lys 2645 2650 2655 Gln Arg Glu Lys Glu Lys Lys Arg Ser Pro Gln Asp Val Glu Val Leu 2660 2665 2670 Lys Thr Thr Glu Leu Phe His Ser Asn Glu Glu Ser Gly Phe Phe 2675 2680 2685 Asn Glu Leu Glu Ala Leu Arg Ala Glu Ser Val Ala Thr Lys Ala Glu 2690 2695 2700 Leu Ala Ser Tyr Lys Glu Lys Ala Glu Lys Leu Gln Glu Glu Leu Leu **2705 2710 2715 2720** Val Lys Glu Thr Asn Met Thr Ser Leu Gln Lys Asp Leu Ser Gln Val 2725 2730 2735 Arg Asp His Leu Ala Glu Ala Lys Glu Lys Leu Ser Ile Leu Glu Lys 2740 2745 2750 Glu Asp Glu Thr Glu Val Gln Glu Ser Lys Lys Ala Cys Met Phe Glu 2755 2760 2765

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2770	Lys Leu	Ser L 2775	ys Ser	Ile Ala	Ser (Gln	Thr	Asp	Gly
Thr Leu Lys Ile 2785	Ser Ser 279		sn Gln	Thr Pro		Ile	Leu	Val	Lys 2800
Asn Ala Gly Ile	Gln Ile 2805	Asn L		Ser Glu 2810	Cys	Ser	Ser	Glu 2815	
Val Thr Glu Ile 282		Gln P	he Thr 2825	_	Ile		Lys 2830		Gln
Glu Leu His Ala 2835	Ala Glu		eu Asp 840	Met Glu		Arg 2845		Ile	Ser
Glu Thr Glu Thr 2850	Leu Lys	Arg G 2855	lu His	Tyr Val	Ala 7 2860	Val	Gln	Leu	Leu
Lys Glu Glu Cys 2865	Gly Thr 287		ys Ala	Val Ile 287		Cys	Leu	Arg	Ser 2880
Lys Glu Gly Ser	Ser Ile 2885	Pro G		Ala His 2890	Ser I	Asp	Ala	Tyr 2895	
Thr Arg Glu Ile 290		Ser A	sp Ser 2905		Asp		Gly 2910		Gly
Ile Tyr Leu Thr 2915		2	920			2925		_	_
Gly Glu Glu Ser 2930	Glu Ser	Ala T 2935	hr Asp	Ser Phe	Pro :	Lys	Lys	Ile	Lys
Gly Leu Leu Arg 2945	Ala Val 295		sn Glu	Gly Met 295		Val	Leu	Ser	Leu 2960
Thr Glu Ser Pro	Tyr Ser 2965	Asp G		Asp His 2970	Ser	Ile	Gln	Gln 2975	
Ser Glu Pro Trp 298	0		2985	_			2990)	
Ser Leu Lys Asp 2995		3	000			30Ō5			
Val Tyr Asp Ser 3010	Ser Gln	Ser H 3015	lis Glu	Ser Phe	Ser 3	Asp	Trp	Arg	Gly
Glu'Leu Leu Leu 3025	Ala Leu 303			303	5		_		3040
						C 7 77			Asp
Leu Leu Ala Ala	3045			3050				3055	i -
Ala Val Gly Leu 306	3045 Leu Asn O	Cys L	eu Glu 3065	3050 Gln Arg	Ile	Gln	Glu 3070	3055 Gln)	Gly
Ala Val Gly Leu 306 Val Glu Tyr Gln 3075	3045 Leu Asn O Ala Ala	Cys L Met G	eu Glu 3065 Slu Cys 1080	3050 Gln Arg Leu Gln	Ile (Gln Ala 3085	Glu 3070 Asp	3055 Gln) Arg	Gly Arg
Ala Val Gly Leu 306 Val Glu Tyr Gln 3075 Ser Leu Leu Ser 3090	3045 Leu Asn O Ala Ala Glu Ile	Cys L Met G 3 Gln A 3095	eu Glu 3065 Iu Cys 080 Ia Leu	3050 Gln Arg Leu Gln His Ala	Ile (Lys : Gln 3100	Gln Ala 3085 Met	Glu 3070 Asp Asn	3055 Gln) Arg Gly	Gly Arg Arg
Ala Val Gly Leu 306 Val Glu Tyr Gln 3075 Ser Leu Leu Ser 3090 Lys Ile Thr Leu 3105	3045 Leu Asn O Ala Ala Glu Ile Lys Arg 311	Cys L Met G 3 Gln A 3095 Glu G	eu Glu 3065 Slu Cys 9080 Lla Leu Sln Glu	3050 Gln Arg Leu Gln His Ala Ser Glu 311	Lys : Gln I 3100 Lys :	Gln Ala 3085 Met Pro	Glu 3070 Asp Asn Ser	3055 Gln) Arg Gly Gln	Gly Arg Arg Glu 3120
Ala Val Gly Leu 306 Val Glu Tyr Gln 3075 Ser Leu Leu Ser 3090 Lys Ile Thr Leu 3105 Leu Leu Glu Tyr	3045 Leu Asn 0 Ala Ala Glu Ile Lys Arg 311 Asn Ile 3125	Cys L Met G 3 Gln A 3095 Glu G 0 Gln G	eu Glu 3065 Glu Cys 080 La Leu Gln Glu	3050 Gln Arg Leu Gln His Ala Ser Glu 311: Gln Ser 3130	Lys Gln I 3100 Lys 5 Gln I	Gln Ala 3085 Met Pro Met	Glu 3070 Asp Asn Ser Leu	3055 Gln) Arg Gly Gln Glu 3135	Gly Arg Arg Glu 3120 Met
Ala Val Gly Leu 306 Val Glu Tyr Gln 3075 Ser Leu Leu Ser 3090 Lys Ile Thr Leu 3105	3045 Leu Asn 0 Ala Ala Glu Ile Lys Arg 311 Asn Ile 3125 Ser Ser	Cys L Met G 3 Gln A 3095 Glu G 0 Gln G	eu Glu 3065 Glu Cys 080 La Leu Gln Glu	3050 Gln Arg Leu Gln His Ala Ser Glu 311: Gln Ser 3130 Arg Ala	Lys Gln I 3100 Lys 5 Gln I	Gln Ala 3085 Met Pro Met	Glu 3070 Asp Asn Ser Leu	3055 Gln Arg Gly Gln Glu 3135 Gln	Gly Arg Arg Glu 3120 Met
Ala Val Gly Leu 306 Val Glu Tyr Gln 3075 Ser Leu Leu Ser 3090 Lys Ile Thr Leu 3105 Leu Leu Glu Tyr Gln Val Glu Leu 314 Gln Leu Ser Ser 3155	3045 Leu Asn O Ala Ala Glu Ile Lys Arg 311 Asn Ile 3125 Ser Ser O Glu Lys	Cys L Met G 3 Gln A 3095 Glu G 0 Gln G Met L Met V 3	eu Glu 3065 Glu Cys 6080 Lla Leu Gln Glu Gln Lys 6ys Asp 3145 Gal Val	3050 Gln Arg Leu Gln His Ala Ser Glu 311: Gln Ser 3130 Arg Ala Ala Glu	Lys : Gln 3100 Lys : Gln Thr	Gln Ala 3085 Met Pro Met Glu Lys 3165	Glu 3070 Asp Asn Ser Leu Leu 3150 Ser	3055 Gln Arg Gly Gln Glu 3135 Gln	Gly Arg Arg Glu 3120 Met Glu Leu
Ala Val Gly Leu 306 Val Glu Tyr Gln 3075 Ser Leu Leu Ser 3090 Lys Ile Thr Leu 3105 Leu Leu Glu Tyr Gln Val Glu Leu 314 Gln Leu Ser Ser 3155 Ala Gln Thr Lys 3170	3045 Leu Asn O Ala Ala Glu Ile Lys Arg 311 Asn Ile 3125 Ser Ser O Glu Lys Leu Glu	Cys L Met G 3 Gln A 3095 Glu G Gln G Met L Met V 3 Leu G 3175	eu Glu 3065 Glu Cys 6080 La Leu Gln Glu Gln Lys 298 Asp 3145 Val 6160 Glu Thr	3050 Gln Arg Leu Gln His Ala Ser Glu 311: Gln Ser 3130 Arg Ala Ala Glu Thr Leu	Lys : Gln : 3100 Lys : 5 Gln : Thr : Leu : Lys : 3180	Gln Ala 3085 Met Pro Met Glu Lys 3165 Ala	Glu 3070 Asp Asn Ser Leu 3150 Ser	3055 Gln Arg Gly Gln Glu 3135 Gln Glu His	Gly Arg Arg Glu 3120 Met Glu Leu Lys
Ala Val Gly Leu 306 Val Glu Tyr Gln 3075 Ser Leu Leu Ser 3090 Lys Ile Thr Leu 3105 Leu Leu Glu Tyr Gln Val Glu Leu 314 Gln Leu Ser Ser 3155 Ala Gln Thr Lys 3170 His Leu Lys Glu 3185	3045 Leu Asn O Ala Ala Glu Ile Lys Arg 311 Asn Ile 3125 Ser Ser O Glu Lys Leu Glu Leu Glu 319	Cys L Met G 3 Gln A 3095 Glu G Gln G Met L Met V 3 Leu G 3175 Ala P	deu Glu 3065 Glu Cys 3080 Gla Leu Gln Glu Gln Lys Asp 3145 Gal Val Glu Thr	3050 Gln Arg Leu Gln His Ala Ser Glu 3111 Gln Ser 3130 Arg Ala Ala Glu Thr Leu Leu Glu 319	Lys : Gln : Solution in the control of the control	Gln Ala 3085 Met Pro Met Glu Lys 3165 Ala	Glu 3070 Asp Asn Ser Leu 3150 Ser Gln Asp	3055 Gln Arg Gly Glu 3135 Gln Glu His	Gly Arg Arg Glu 3120 Met Glu Leu Lys Thr 3200
Ala Val Gly Leu 306 Val Glu Tyr Gln 3075 Ser Leu Leu Ser 3090 Lys Ile Thr Leu 3105 Leu Leu Glu Tyr Gln Val Glu Leu 314 Gln Leu Ser Ser 3155 Ala Gln Thr Lys 3170 His Leu Lys Glu 3185 Asp Glu Val His	3045 Leu Asn O Ala Ala Glu Ile Lys Arg 311 Asn Ile 3125 Ser Ser O Glu Lys Leu Glu Leu Glu 319 Leu Leu 3205	Cys L Met G 3 Gln A 3095 Glu G 0 Gln G Met L Met V 3 Leu G 3175 Ala P 0 Asn A	eu Glu 3065 clu Cys 6080 cla Leu cln Glu cln Lys 6ys Asp 3145 cal Val 6160 clu Thr 6he Arg	3050 Gln Arg Leu Gln His Ala Ser Glu 311: Gln Ser 3130 Arg Ala Ala Glu Thr Leu Leu Glu 319: Leu Ala 3210	Lys : Gln 3100 Lys : Gln Thr Leu : Lys : 3180 Val : Ser	Gln Ala 3085 Met Pro Met Glu Lys 3165 Ala Lys	Glu 3070 Asp Asn Ser Leu 3150 Ser Gln Asp	3055 Gln Arg Gly Gln Glu 3135 Gln Glu His Lys 3215	Gly Arg Arg Glu 3120 Met Glu Leu Lys Thr 3200 Lys
Ala Val Gly Leu 306 Val Glu Tyr Gln 3075 Ser Leu Leu Ser 3090 Lys Ile Thr Leu 3105 Leu Leu Glu Tyr Gln Val Glu Leu 314 Gln Leu Ser Ser 3155 Ala Gln Thr Lys 3170 His Leu Lys Glu 3185	3045 Leu Asn O Ala Ala Glu Ile Lys Arg 311 Asn Ile 3125 Ser Ser O Glu Lys Leu Glu 119 Leu Glu 219 Leu Leu 3205 Gln Trp	Cys L Met G 3 Gln A 3095 Glu G 0 Gln G Met L Met V 3 Leu G 3175 Ala P 0 Asn A	deu Glu 3065 Glu Cys 6080 Gla Leu Gln Glu Gln Lys 618 Asp 3145 Gal Val Glu Thr 648 Arg 659 Thr 660 Glu 3225	3050 Gln Arg Leu Gln His Ala Ser Glu 3110 Gln Ser 3130 Arg Ala Ala Glu Thr Leu Leu Glu 3190 Leu Ala 3210 Lys Glu	Lys : Gln I 3100 Lys : Gln I Thr (Leu : Lys : Lys : Ser (Lys :	Gln Ala 3085 Met Pro Met Glu Lys 3165 Ala Lys Glu Ala	Glu 3070 Asp Asn Ser Leu 3150 Ser Gln Asp Gln Lys 3230	3055 Gln Arg Gly Gln Glu 3135 Gln Glu His Lys Lys 3215 Leu	Gly Arg Glu 3120 Met Glu Leu Lys Thr 3200 Lys Gly

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Leu Glu Ser Gln Lys Gln Arg Asn Leu Gln Leu Asn Leu Glu 3250 3255 3260 3255 3260 3275 3280 3275 3280 3275 3280 3275 3280 3285 3280 3285 3280 3285 3280 3290 3295 3285 3280 3290 3295 3285 3280 3290 3295 3285 3300 3300 3305 3310 3305 3310 3315 3320 3325 3325 3330 3330 3335 3330 3330 3335 3330 3335 3330 3335 3330			3235				3240					3245				
3275 3270 3275 3280 3295 3290 3295 3295 3290 3295	Leu			Gln	Lys	Gln			Leu	Gln	Leu			Leu	Leu	Glu
S285 S290 S295 S290 S295 S296 S296 S296 S296 S296 S296 S296 S297	3265	5				3270)				327	5				3280
Ser Ser Thr Leu Asp Arg Glu Arg Glu Leu His Ala Gln Leu Gln Ser 3315 Ser Asp Gly Thr Gly Gln Ser Arg Pro Pro Leu Pro Ser Glu Asp Leu 3330 Say 3345 Leu Lys Glu Leu Gln Lys Gln Leu Glu Glu Lys His Ser Arg Ile Val 3345 Glu Leu Leu Asn Glu Thr Glu Lys Tyr Lys Leu Asp Ser Leu Gln Thr 3365 Arg Gln Gln Met Glu Lys Asp Arg Gln Val His Arg Lys Thr Leu Gln 3375 Arg Gln Gln Met Glu Lys Asp Arg Gln Val His Arg Lys Thr Leu Gln 3395 Thr Glu Gln Glu Ala Asn Thr Glu Gly Gln Lys Lys Met His Glu Leu Gln A345 Gln Ser Lys Val Glu Asp Leu Gln Arg Gln Leu Glu Glu Lys Arg Gln 3405 Gln Ser Lys Val Glu Asp Leu Gln Arg Gln Leu Glu Glu Lys Arg Gln 3415 Gln Val Tyr Lys Leu Asp Leu Gln Arg Gln Arg Leu Gln Gly Ile Met 3425 Gln Glu Phe Gln Lys Gln Glu Leu Glu Glu Glu Lys Arg Gln 3455 Arg Arg Ile Leu Tyr Gln Asn Leu Asn Glu Fro Thr Thr Trp Ser Leu 3465 Arg Arg Tle Leu Tyr Gln Asn Leu Asn Glu Fro Thr Thr Trp Ser Leu 3465 Thr Ser Asp Arg Thr Arg Asn Trp Val Leu Gln Gln Lys Ile Glu Gly 3475 Glu Thr Lys Glu Ser Asn Tyr Ala Lys Leu Ile Glu Met Asn Gly Gly 3495 Gly Thr Gly Cys Asn His Glu Leu Glu Met Ile Arg Gln Lys Leu Gln Gly Jaks Ser Jaks Ser Leu Gln Gly Ile Gly 3475 Gly Thr Gly Cys Asn His Glu Leu Glu Met Ile Arg Gln Lys Leu Gln Gly Jaks Ser Glu Arg 3555 Gly Gln Fhe Glu Thr Ala Asp Asp Glu Met Ile Arg Gln Lys Leu Gln Gly 3555 Cys Val Ala Ser Lys Leu Gln Val Leu Gln Lys Leu Thr Gly Gln Gln Gly 3555 Gly Glu Gln Fle Glu Thr Ala Asp Asp Glu Asp Phe Ile Trp Val Gln Glu Gly 3555 Gly Glu Glu Fro Ser Leu Val Ser Pro Ser Thr Ser Cys Gly Ser Leu Ser Siso 3550 Gly Glu Gln The Glu Glu Lys Asn Asp Leu Arg Asn Met Val Met Lys Leu 3600 Glu Glu Gln Ile Arg Trp Tyr Arg Gln Thr Gly Ala Gly Arg Asp Asn 3655 Glu Glu Gln Ile Arg Trp Tyr Arg Gln Thr Gly Ala Gly Arg Asp Asn 3655 Glu Glu Gln Ile Arg Trp Tyr Arg Glu Thr Gly Lys Leu Thr Leu Gln Lys 3650 Ser Leu Lys Arg Ala Glu Ala Glu Val Trp Lys Leu Lys Ala Glu Leu Glo	Arg	Met	Leu	Tyr	_		Gln	Leu	Ser			Gln	Gly	Arg		
Sat Sap Gly Thr Gly Gln Ser Arg Pro Pro Leu Pro Ser Glu Asp Leu 3330 Leu Lys Glu Leu Gln Lys Gln Leu Gln Lys Gln Leu Glu Glu Lys His Ser Arg Ile Val 3345 Glu Leu Leu Asn Glu Thr Glu Lys Tyr Lys Leu Asp Ser Leu Gln Thr 3365 Arg Gln Gln Met Glu Lys Asp Arg Gln Val His Arg Lys Thr Leu Gln 3375 Arg Gln Gln Met Glu Lys Asp Arg Gln Val His Arg Lys Thr Leu Gln 3380 Thr Glu Gln Glu Ala Asn Thr Glu Gly Gln Lys Lys Met His Glu Leu 3395 Thr Glu Gln Gln Asp Leu Gln Arg Gln Lys Lys Met His Glu Leu 3395 Gln Ser Lys Val Glu Asp Leu Gln Arg Gln Leu Glu Glu Lys Arg Gln 3415 Gln Val Tyr Lys Leu Asp Leu Glu Gly Gln Arg Leu Gln Gly Leu 3425 Gln Glu Phe Gln Lys Gln Glu Leu Glu Arg Glu Glu Lys Arg Gln 3425 Arg Arg Ile Leu Tyr Gln Asn Leu Asn Glu Pro Thr Thr Trp Ser Leu 3460 Thr Ser Asp Arg Thr Arg Asn Trp Val Leu Gln Gln Lys Ile Glu Gly 3475 Glu Thr Lys Glu Ser Asn Tyr Val Lys Leu Gln Gln Lys Ile Glu Gly 3475 Gly Thr Gly Cys Asn His Glu Leu Glu Met 3485 Gly Thr Gly Cys Asn His Glu Leu Glu Met 11e Arg Gln Lys Leu Gln Gly Gly 3495 Gly Thr Gly Cys Asn His Glu Leu Glu Met 11e Arg Gln Lys Leu Gln Gly 3550 Cys Val Ala Ser Lys Leu Gln Val Leu Pro Gln Lys Asn Gly Gly 3495 Asn Ile Asp Glu Ir The Ala Asp Asp Glu Asp Phe Ile Trp Val Glu Glu Glu Cys Asp 3550 Thr Glu Glu Thr Ala Asp Asp Glu Asp Phe Ile Trp Val Glu Glu Glu Glu Cys Asp Asp Glu Asp Phe Ile Trp Val Glu Glu Glu Cys Asp Asp Glu Asp Cys Glu Asp Cys Glu Glu Glu Cys Asp Asp Asp Glu Asp Cys Glu Glu Glu Cys Asp Asp Asp Glu Glu Cys Asp Asp Asp Glu Glu Glu Cys Asp Asp Asp Glu Glu Cys Asp Asp Asp Glu Glu Glu Cys Asp Asp Asp Glu Glu Glu Cys Asp Asp Asp Glu Gly Ala Glu Ala Glu Leu Glo Glu Glu Cys Glu Val Trp Asp Arg Glu Cys	Glu	Leu	Gln			Leu	Glu	Ser			Val	Arg	Ile			Met
3330			331	5	_	_		3320)				332	5		
3355		3330)				3335	5				3340)			
Selic Leu Leu Asn Glu Thr Glu Lys Tyr Lys Leu Asp Ser Leu Gln Thr 3365 3370 3370 3370 3380			Glu	Leu	Gln			Leu	Glu	Glu			Ser	Arg	Ile	
Arg Gln Gln Met Glu Lys Asp Arg Gln Glu Glu Glu Glu Glu Glu Glu Glu Glu Lys Met His Glu Leu Glu Glu Leu Glu Sad 3440 Glu Glu Glu Glu Glu Glu Glu Glu Sad 3440 Glu Glu Glu Glu Sad Glu Sad Glu Sad Asp Asp </td <td></td> <td></td> <td>Leu</td> <td>Asn</td> <td></td> <td>Thr</td> <td></td> <td>Lys</td> <td>Tyr</td> <td>_</td> <td>Leu</td> <td></td> <td>Ser</td> <td>Leu</td> <td></td> <td>Thr</td>			Leu	Asn		Thr		Lys	Tyr	_	Leu		Ser	Leu		Thr
Say	Arg	Gln	Gln			Lys	Asp	Arg		Val		Arg	Lys		Leu	
3410			3395	5				3400)		_		340	5		
3425		3410)				3415	5				3420)			
Arg Arg Ile Leu Tyr Gln Asn Leu Asn Glu Pro Thr Thr Try Ser Leu 3465			Tyr	Lys	Leu			Glu	Gly	Gln			Gln	Gly	Ile	
The Ser Asp Arg The Arg Asn Trp Val Leu Gln Gln Lys Ile Glu Gly 3475 Glu The Lys Glu Ser Asn Tyr Ala Lys Leu Ile Glu Met Asn Gly Gly 3490 Gly The Gly Cys Asn His Glu Leu Glu Met Ile Arg Gln Lys Leu Gln 3505 Gly The Gly Cys Asn His Glu Leu Glu Met Ile Arg Gln Lys Leu Gln 3505 Cys Val Ala Ser Lys Leu Gln Val Leu Pro Gln Lys Ala Ser Glu Arg 3535 Leu Gln Phe Glu The Ala Asp Asp Glu Asp Phe Ile Trp Val Gln Glu 3550 Asn Ile Asp Glu Ile Ile Leu Gln Leu Gln Lys Leu The Gly Gly Gly 3555 Gly Glu Glu Pro Ser Leu Val Ser Pro Ser The Ser Cys Gly Ser Leu 3570 The Glu Arg Leu Arg Gln Asn Ala Glu Leu The Gly His Ile Ser 3585 Gly Glu Glu Pro Ser Leu Arg Gln Asn Ala Glu Leu The Gly His Ile Ser 3585 Gly Glu Glu Fro Ser Leu Arg Gln Asn Ala Glu Leu The Gly His Ile Ser 3585 Gly Glu Glu Fro Ser Leu Arg Gln Asn Ala Glu Leu The Gly His Ile Ser 3600 Gln Leu The Glu Glu Lys Asn Asp Leu Arg Asn Met Val Met Lys Leu 3605 Glu Glu Glu Ile Arg Trp Tyr Arg Gln The Gly Ala Gly Arg Asp Asn 3620 Ser Ser Arg Phe Ser Leu Asn Gly Gly Ala Asn Ile Glu Ala Ile Ile 3635 Ser Ser Glu Lys Arg Ala Glu Ala Glu Val Tyr Lys Leu The Gly Ala Glu Leu 11 Leu Glo Lys 3655 Ser Leu Lys Arg Ala Glu Ala Glu Val Tyr Lys Leu The Gly Ala Glu Leu 3665 Ser Leu Lys Arg Ala Glu Ala Glu Val Tyr Lys Leu The Glu His Val 3665 The Leu Lys Arg Arg Ala Glu Ala Glu Val Tyr Lys Leu Tyr Asp Ser Glu His Val 3665 The Leu Lys Arg Ile Tyr Gly Lys Tyr Leu Arg Ala Glu Ser Phe Arg	Gln	Glu	Phe	Gln			Glu	Leu	Glu	_		Glu	Lys	Arg		
S475	Arg	Arg	Ile			Gln	Asn	Leu			Pro	Thr	Thr	_		Leu
Gly Thr Gly Cys Asn His Glu Leu Glu Met Ile Arg Gln Lys Leu Gln 3505	Thr	Ser			Thr	Arg	Asn			Leu	Gln	Gln	_		Glu	Gly
3505	Glu			Glu	Ser	Asn			Lys	Leu	Ile			Asn	Gly	Gly
Let 3525			Gly	Cys	Asn			Leu	Glu	Met		-	Gln	Lys	Leu	
Asn Ile Asp Glu Ile Ile Leu Gln Leu Gln Lys Leu Thr Gly Gln Gln Gln 35555 Gly Glu Glu Pro Ser Leu Val Ser Pro Ser Thr Ser Cys Gly Ser Leu 3570	Cys	Val	Ala	Ser			Gln	Val	Leu			Lys	Ala	Ser		_
Gly Glu Glu Pro Ser Leu Val Ser Pro Ser Thr Ser Cys Gly Ser Leu 3570	Leu	Gln	Phe			Ala	Asp	Asp			Phe	Ile	Trp			Glu
Thr Glu Arg Leu Leu Arg Gln Asn Ala Glu Leu Thr Gly His Ile Ser 3585			3555	5				3560)				356	5		
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	Thr	Leu	Lys		Ile		Gly	Lys		Leu		Ala	Glu		Phe	

Lys Ala Leu Ile Tyr Gln Lys Lys Tyr Leu Leu Leu Leu Leu Gly Gly 3715 3720 3725

Phe Gln Glu Cys Glu Asp Ala Thr Leu Ala Leu Leu Ala Arg Met Gly 3730 3740

Gly Gln Pro Ala Phe Thr Asp Leu Glu Val Ile Thr Asn Arg Pro Lys 3745 3750 3755 3760

Gly Phe Thr Arg Phe Arg Ser Ala Val Arg Val Ser Ile Ala Ile Ser 3765 3770 3775

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Ser Ile Asn Ile Asn Arg Asp Gly Phe Gly Leu Asn Gln Gly Ala Glu 3795 3800 3805

Lys Thr Asp Ser Phe Tyr His Ser Ser Gly Gly Leu Glu Leu Tyr Gly 3810 3815 3820

Glu Pro Arg His Thr Thr Tyr Arg Ser Arg Ser Asp Leu Asp Tyr Ile 3825 3830 3835 3840

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Met Arg Arg 3905

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<213> Homo sapiens

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Lys	Asn 370	Gln	Glu	Ile	Lys	Asn 375	Met	ГÀЗ	Leu	Glu	Leu 380	Thr	Asn	Ser	Lys
Gln 385	Lys	Glu	Arg	Gln	Ser 390	Ser	Glu	Glu	Ile	Lys 395	Gln	Leu	Met	Gly	Thr 400
Val	Glu	Glu	Leu	Gln 405	Lys	Arg	Asn	His	Lys 410	Asp	Ser	Gln	Phe	Glu 415	Thr
Asp	Ile	Val	Gln 420	Arg	Met	Glu	Gln	Glu 425	Thr	Gln	Arg	Lys	Leu 430	Glu	Gln
Leu	Arg	Ala 435		Leu	Asp	Glu	Met 440		Gly	Gln	Gln	Ile 445		Gln	Met
Lys	Gln 450	Glu	Leu	Ile	Arg	Gln 455		Met	Ala	Gln	Met 460		Glu	Met	Lys
Thr 465		His	Lys	Gly	Glu 470		Glu	Asn	Ala	Leu 475		Ser	Tyr	Ser	Asn 480
	Thr	Val	Asn	Glu 485	Asp	Gln	Ile	Lys	Leu 490	Met	Asn	Val	Ala	Ile 495	
Glu	Leu	Asn	Ile 500	Lys	Leu	Gln	Asp	Thr 505	Asn	Ser	Gln	Lys	Glu 510	Lys	Leu
Lys	Glu	Glu 515	Leu	Gly	Leu	Ile	Leu 520	Glu	Glu	Lys	Cys	Ala 525		Gln	Arg
Gln	Leu 530	Glu	Asp	Leu	Val	Glu 535	G1u	Leu	Ser	Phe	Ser 540	Arg	Glu	Gln	Ile
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Ala	His	Lys	Ser	Leu 565	Ser	Thr	Val	Glu	Asp 570	Leu	Lys	Ala	Glu	Ile 575	Val
Ser	Ala	Ser	Glu 580	Ser	Arg	Lys	Glu	Leu 585	Glu	Leu	Lys	His	Glu 590	Ala	Glu
Val	Thr	Asn 595	Tyr	Lys	Ile	Lys	Leu 600	Glu	Met	Leu	Glu	Lys 605	Glu	Lys	Asn
Ala	Val 610	Leu	Asp	Arg	Met	Ala 615	Glu	Ser	Gln	Glu	Ala 620	Glu	Leu	Glu	Arg
Leu 625	Arg	Thr	Gln	Leu	Leu 630	Phe	Ser	His	Glu	Glu 635	Glu	Leu	Ser	Lys	Leu 640
Lys	Glu	Asp	Leu	Glu 645	Ile	Glu	His	Arg	Ile 650	Asn	Ile	Glu	Lys	Leu 655	Lys
			660			_	_	665		Ile			670		
		675					680			Phe		685			
Ile		Lys			Gln					Ile	Ser 700		Leu	Lys	Asp
Leu 705	Gln	Gln	Ser	Leu	Val 710	Asn	Ser	Lys	Ser	Glu 715	Glu	Met	Thr	Leu	Gln 720
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Glu	Lys	Gly	Thr 740	Leu	Glu	Gln	Glu	Val 745	Gln	Glu	Leu	Gln	Leu 750	Lys	Thr
Glu	Leu	Leu 755	Glu	Lys	Gln	Met	Lys 760	Glu	Lys	Glu	Asn	Asp 765	Leu	Gln	Glu
Lys	Phe 770	Ala	Gln	Leu	Glu	Ala 775	Glu	Asn	Ser	Ile	Leu 780	Lys	Asp	Glu	Lys
785					790					Thr 795					800
				805					810	Ser				815	
Val	Trp	Glu	Lys 820	Glu	Ile	Glu	Ile	Leu 825	Ile	Glu	Glu	Asn	Glu 830	Asp	Leu
Lys	Gln	Gln	Cys	Ile	Gln	Leu	Asn	Glu	Glu	Ile	Glu	Lys	Gln	Arg	Asn

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Asp His Leu Pro Ser Val Thr Lys Glu Ser Ser Leu Arg Ala Thr Gln 1075 1080 1085 Pro Ser Glu Asn Asp Lys Leu Gln Lys Glu Leu Asn Val Leu Lys Ser 1090 1095 1100 Glu Gln Asn Asp Leu Arg Leu Gln Met Glu Ala Gln Arg Ile Cys Leu 1105 1110 1115 Ser Leu Val Tyr Ser Thr His Val Asp Gln Val Arg Glu Tyr Met Glu 1125 1130 1135 Asn Glu Lys Asp Lys Ala Leu Cys Ser Leu Lys Glu Glu Leu Ile Phe 1140 1145 Ala Gln Glu Lys Ile Lys Glu Leu Gln Lys Ile His Gln Leu Glu 1155 1160 1165 Leu Gln Thr Met Lys Thr Gln Glu Thr Gly Asp Glu Gly Lys Pro Leu 1175 1180 His Leu Leu Ile Gly Lys Leu Gln Lys Ala Val Ser Glu Glu Cys Ser 1185 1190 1195 1200 Tyr Phe Leu Gln Thr Leu Cys Ser Val Leu Gly Glu Tyr Tyr Thr Pro 1205 1210 1215 Ala Leu Lys Cys Glu Val Asn Ala Glu Asp Lys Glu Asn Ser Gly Asp 1220 1225 1230 Tyr Ile Ser Glu Asn Glu Asp Pro Glu Leu Gln Asp Tyr Arg Tyr Glu 1235 1240 1245 Val Gln Asp Phe Gln Glu Asn Met His Thr Leu Leu Asn Lys Val Thr 1250 1255 1260 · Glu Glu Tyr Asn Lys Leu Leu Val Leu Gln Thr Arg Leu Ser Lys Ile 1265 1270 1275 1280 Trp Gly Gln Gln Thr Asp Gly Met Lys Leu Glu Phe Gly Glu Glu Asn 1285 1290 1295 Leu Pro Lys Glu Glu Thr Glu Phe Leu Ser Ile His Ser Gln Met Thr 1300 1305

Asn Leu Glu Asp Ile Asp Val Asn His Lys Ser Lys Leu Ser Ser Leu 1315 1320 1325 Gln Asp Leu Glu Lys Thr Lys Leu Glu Glu Gln Val Gln Glu Leu Glu 1330 1335 1340 Ser Leu Ile Ser Ser Leu Gln Gln Gln Leu Lys Glu Thr Glu Gln Asn 1345 1350 1355 1360 Tyr Glu Ala Glu Ile His Cys Leu Gln Lys Arg Leu Gln Ala Val Ser 1365 1370 1375 Glu Ser Thr Val Pro Pro Ser Leu Pro Val Asp Ser Val Val Ile Thr 1380 1385 1390 Glu Ser Asp Ala Gln Arg Thr Met Tyr Pro Gly Ser Cys Val Lys Lys 1395 1400 Asn Ile Asp Gly Thr Ile Glu Phe Ser Gly Glu Phe Gly Val Lys Glu 1410 1415 1420 Glu Thr Asn Ile Val Lys Leu Leu Glu Lys Gln Tyr Gln Glu Gln Leu 1430 1435 1440 Glu Glu Val Ala Lys Val Ile Val Ser Met Ser Ile Ala Phe Ala 1445 1450 1455 Gln Gln Thr Glu Leu Ser Arg Ile Ser Gly Gly Lys Glu Asn Thr Ala 1460 1465 1470 Ser Ser Lys Gln Ala His Ala Val Cys Gln Gln Glu Gln His Tyr Phe 1475 1480 1485 Asn Glu Met Lys Leu Ser Gln Asp Gln Ile Gly Phe Gln Thr Phe Glu 1490 1495 1500 Thr Val Asp Val Lys Phe Lys Glu Glu Phe Lys Pro Leu Ser Lys Glu 1510 1515 1520 Leu Gly Glu His Gly Lys Glu Ile Leu Leu Ser Asn Ser Asp Pro His 1525 1530 1535 Asp Ile Pro Glu Ser Lys Asp Cys Val Leu Thr Ile Ser Glu Glu Met 1540 1545 1550 Phe Ser Lys Asp Lys Thr Phe Ile Val Arg Gln Ser Ile His Asp Glu 1555 1560 1565 Ile Ser Val Ser Ser Met Asp Ala Ser Arg Gln Leu Met Leu Asn Glu 1570 1575 1580 Glu Gln Leu Glu Asp Met Arg Gln Glu Leu Val Arg Gln Tyr Gln Glu 1590 1595 His Gln Gln Ala Thr Glu Leu Leu Arg Gln Ala His Met Arg Gln Met 1605 1610 1615 Glu Arg Gln Arg Glu Asp Gln Glu Gln Leu Gln Glu Glu Ile Lys Arg 1620 1625 1630 Leu Asn Arg Gln Leu Ala Gln Arg Ser Ser Ile Asp Asn Glu Asn Leu 1635 1640 1645 Val Ser Glu Arg Glu Arg Val Leu Leu Glu Glu Leu Glu Ala Leu Lys 1655 1660 Gln Leu Ser Leu Ala Gly Arg Glu Lys Leu Cys Cys Glu Leu Arg Asn 1670 1675 1680 Ser Ser Thr Gln Thr Gln Asn Gly Asn Glu Asn Gln Gly Glu Val Glu 1685 1690 Glu Gln Thr Phe Lys Glu Lys Glu Leu Asp Arg Lys Pro Glu Asp Val 1700 1705 Pro Pro Glu Ile Leu Ser Asn Glu Arg Tyr Ala Leu Gln Lys Ala Asn 1720 Asn Arg Leu Leu Lys Ile Leu Leu Glu Val Val Lys Thr Thr Ala Ala 1735 1740 Val Glu Glu Thr Ile Gly Arg His Val Leu Gly Ile Leu Asp Arg Ser 1750 1755 Ser Lys Ser Gln Ser Ser Ala Ser Leu Ile Trp Arg Ser Glu Ala Glu 1770 Ala Ser Val Lys Ser Cys Val His Glu Glu His Thr Arg Val Thr Asp

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Leu Val 1825	Arg Ser	Gly Phe 183	Ala Gly 0	Thr Glu	Ile Asp 1835	Pro Gl	u Asn	Glu 1840
Glu Leu	Met Leu	Asn Ile 1845	Ser Ser	Arg Leu 185		Ala Va	1 Glu 185	_
Leu Leu	Glu Ala 186		Glu Thr	Ser Ser 1865	Gln Leu		s Ala 70	Lys
Val Thr	Gln Thr 1875	Glu Leu	Met Arg 188		Phe Arg	Gln Ly 1885	s Gln	Glu
189	0	_	Cys Gln 1895		190	0	_	
1905		191			1915		_	1920
		1925	Tyr Ala	193	0		193	5
	194	0	Aṣp Ile	1945	_	19	50	
	1955		Leu Gln 196	0		1965		
197	0		Leu Leu 1975		198	0		
1985		199			1995			2000
		2005	Glu Val	201	0	_	201	5
	202	0	Val Lys	2025		20	30	
	2035		Glu Leu 204	0		2045		
205	0		Asn Gln 2055		206	0		
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	210	0	Ile Ser	2105		21	10	
	2115		Lys Glu 212	0		2125		
213	0		Leu Gln 2135		214	0		
2145		215		_	2155			2160 "7
		2165	His Phe	217	0		217	õ
	218	0	Leu Gln	2185	_	21	90	, -
	2195		Asn Leu 220	0		2205		_
221	0		Asn Glu 2215		222	0		
2225		223			2235			2240
eru era	Asn Lys	Leu Phe 2245	Lys Asp	Asp Met 225		ьеи Gl	y Leu 225	

Ile Lys Glu Ser Asp Ala Met Ser Thr Gln Asp Gln His Val Leu Phe 2260 2265 2270 Gly Lys Phe Ala Gln Ile Ile Gln Glu Lys Glu Val Glu Ile Asp Gln 2275 2280 2285 Leu Asn Glu Gln Val Thr Lys Leu Gln Gln Leu Lys Ile Thr Thr 2290 2295 2300 Asp Asn Lys Val Ile Glu Glu Lys Asn Glu Leu Ile Arg Asp Leu Glu 2305 2310 2315 2320 Thr Gln Ile Glu Cys Leu Met Ser Asp Gln Glu Cys Val Lys Arg Asn 2325 2330 2335 Arg Glu Glu Glu Ile Glu Gln Leu Asn Glu Val Ile Glu Lys Leu Gln 2340 2345 2350 Gln Glu Leu Ala Asn Ile Gly Gln Lys Thr Ser Met Asn Ala His Ser 2355 2360 2365 Leu Ser Glu Glu Ala Asp Ser Leu Lys His Gln Leu Asp Val Val Ile 2370 2375 2380 Ala Glu Lys Leu Ala Leu Glu Gln Val Glu Thr Ala Asn Glu Glu 2390 2395 2400 Met Thr Phe Met Lys Asn Val Leu Lys Glu Thr Asn Phe Lys Met Asn 2405 2410 2415 Gln Leu Thr Gln Glu Leu Phe Ser Leu Lys Arg Glu Arg Glu Ser Val 2420 2425 2430 Glu Lys Ile Gln Ser Ile Pro Glu Asn Ser Val Asn Val Ala Ile Asp 2435 2440 2445 His Leu Ser Lys Asp Lys Pro Glu Leu Glu Val Val Leu Thr Glu Asp 2450 2455 2460 Ala Leu Lys Ser Leu Glu Asn Gln Thr Tyr Phe Lys Ser Phe Glu Glu **2465 2470 2475 2480** Asn Gly Lys Gly Ser Ile Ile Asn Leu Glu Thr Arg Leu Leu Gln Leu 2485 2490 2495 Glu Ser Thr Val Ser Ala Lys Asp Leu Glu Leu Thr Gln Cys Tyr Lys 2500 2505 2510 Gln Ile Lys Asp Met Gln Glu Gln Gly Gln Phe Glu Thr Glu Met Leu 2515 2520 2525 Gln Lys Lys Ile Val Asn Leu Gln Lys Ile Val Glu Glu Lys Val Ala 2530 2535 2540 Ala Ala Leu Val Ser Gln Ile Gln Leu Glu Ala Val Gln Glu Tyr Ala 2545 2550 2555 Lys Phe Cys Gln Asp Asn Gln Thr Ile Ser Ser Glu Pro Glu Arg Thr 2565 2570 2575 Asn Ile Gln Asn Leu Asn Gln Leu Arg Glu Asp Glu Leu Gly Ser Asp 2580 2585 2590 Ile Ser Ala Leu Thr Leu Arg Ile Ser Glu Leu Glu Ser Gln Val Val 2595 2600 2605 Glu Met His Thr Ser Leu Ile Leu Glu Lys Glu Gln Val Glu Ile Ala 2610 2615 2620 Glu Lys Asn Val Leu Glu Lys Glu Lys Lys Leu Leu Glu Leu Gln Lys 2630 2635 Leu Leu Glu Gly Asn Glu Lys Lys Gln Arg Glu Lys Glu Lys Arg 2645 2650 2655 Ser Pro Gln Asp Val Glu Val Leu Lys Thr Thr Thr Glu Leu Phe His 2660 2665 Ser Asn Glu Glu Ser Gly Phe Phe Asn Glu Leu Glu Ala Leu Arg Ala 2680 Glu Ser Val Ala Thr Lys Ala Glu Leu Ala Ser Tyr Lys Glu Lys Ala 2695 2690 2700 Glu Lys Leu Gln Glu Glu Leu Leu Val Lys Glu Thr Asn Met Thr Ser 2710 2715 Leu Gln Lys Asp Leu Ser Gln Val Arg Asp His Leu Ala Glu Ala Lys

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3685 3690 3695

Tyr Leu Arg Ala Glu Ser Phe Arg Lys Ala Leu Ile Tyr Gln Lys Lys
3700 3705 3710

Tyr Leu Leu Leu Leu Gly Gly Phe Gln Glu Cys Glu Asp Ala Thr 3715 3720 3725

Leu Ala Leu Leu Ala Arg Met Gly Gln Pro Ala Phe Thr Asp Leu 3730 3740

Glu Val Ile Thr Asn Arg Pro Lys Gly Phe Thr Arg Phe Arg Ser Ala 3745 3750 3755 3760

Val Arg Val Ser Ile Ala Ile Ser Arg Met Lys Phe Leu Val Arg Arg
3765 3770 3775

Trp His Arg Val Thr Gly Ser Val Ser Ile Asn Ile Asn Arg Asp Gly 3780 3785 3790

Phe Gly Leu Asn Gln Gly Ala Glu Lys Thr Asp Ser Phe Tyr His Ser 3795 3800 3805

Ser Gly Gly Leu Glu Leu Tyr Gly Glu Pro Arg His Thr Thr Tyr Arg 3810 3815 3820

Ser Arg Ser Asp Leu Asp Tyr Ile Arg Ser Pro Leu Pro Phe Gln Asn 3825 3830 3835 3840

Arg Tyr Pro Gly Thr Pro Ala Asp Phe Asn Pro Gly Ser Leu Ala Cys 3845 3850 3855

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Leu	Ala	Gln	Phe 20	Arg	Gln	Arg	Lys	Ala 25	Gln	Ser	Asp	Gly		Ser	Pro	
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Val	Ser 50	Ala	His	His	Asp	Leu 55	Asn	Ile	Asp	Gln	Ser 60	Gln	Cys	Asn	Glu	
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Second S	Glu	Arg	Leu	Ile		Leu	Asp	Ser	Ile		Ser	Lys	Ser	Lys	_	Ser
## Sas	Val	Trp	Glu		Glu	Ile	Glu	Ile		Ile	Glu	Glu	Asn		Asp	Leu
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Val Gln Ser Cys Asp Thr Gln Val Ser Leu Leu Asp Gly Val Val 1010 Thr Met Thr Ser Arg Gly Ala Glu Gly Ser Val Ser Lys Val Asn Lys 1025 Thr Met Thr Ser Arg Gly Ala Glu Gly Ser Val Ser Lys Val Asn Lys 1025 Ser Phe Gly Glu Glu Ser Lys Ile Met Val Glu Asp Lys Val Ser Phe 1045 Glu Asn Met Thr Val Gly Glu Glu Ser Lys Ile Met Val Glu Asp Lys Val Ser Phe 1065 Glu Asn Met Thr Val Gly Glu Glu Ser Lys Gln Glu Gln Leu Ile Leu 1065 Asp His Leu Pro Ser Val Thr Lys Glu Ser Ser Leu Arg Ala Thr Gln 1075 Pro Ser Glu Asn Asp Lys Leu Gln Lys Glu Leu Asn Val Leu Lys Ser 1090 Glu Gln Asn Asp Lu Arg Leu Gln Lys Glu Leu Asn Val Leu Lys Ser 1090 Glu Gln Asn Asp Lys Ala Leu Gln Met Glu Ala Gln Arg Ile Cys Leu 1115 Ser Leu Val Tyr Ser Thr His Val Asp Gln Val Arg Glu Tyr Met Glu 1125 Asn Glu Lys Asp Lys Ala Leu Cys Ser Leu Lys Glu Glu Leu Ile Phe 1140 Ala Gln Glu Glu Lys Ile Lys Glu Leu Gln Lys Ile His Gln Leu Glu 1155 Leu Gln Thr Met Lys Thr Gln Glu Heu Gln Lys Ile His Gln Leu Glu 1170 His Leu Leu Ile Gly Lys Leu Gln Lys Ala Val Ser Glu Glu Cys Ser 1185 Leu Gln Thr Met Lys Thr Gln Glu Thr Gly Asp Glu Glu Tyr Thr Pro 1205 Tyr Phe Leu Gln Thr Leu Cys Ser Val Leu Gln Asp Lys Pro Leu 1215 Ala Leu Lys Cys Glu Val Asn Ala Glu Asp Lys Glu Asn Ser Gly Asp 1220 Tyr Ile Ser Glu Asn Glu Asp Pro Glu Leu Gln Asp Tyr Arg Tyr Glu 1235 Tyr Ile Ser Glu Asn Glu Asp Met His Thr Leu Leu Asn Lys Val Thr				980					985					990		
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Glu Asn Met Thr Val Gly Glu Glu Ser Lys Gln Glu Gln Leu Ile Leu 1060 1065 1085 1070 Asp His Leu Pro Ser Val Thr Lys Glu Ser Ser Leu Arg Ala Thr Gln 1075 1080 1085 1085 Pro Ser Glu Asn Asp Lys Leu Gln Lys Glu Leu Asn Val Leu Lys Ser 1090 1095 1100 Glu Gln Asn Asp Leu Arg Leu Gln Met Glu Ala Gln Arg Ile Cys Leu 1105 1115 1120 Ser Leu Val Tyr Ser Thr His Val Asp Glu Val Arg Glu Tyr Met Glu 1125 1130 1135 Asn Glu Lys Asp Lys Ala Leu Cys Ser Leu Lys Glu Glu Leu Ile Phe 1140 1155 1150 Ala Gln Glu Glu Lys Ile Lys Glu Leu Gln Lys Ile His Gln Leu Glu 1155 1160 1165 Leu Gln Thr Met Lys Thr Gln Glu Thr Gly Asp Glu Gly Lys Pro Leu 1170 1175 His Leu Leu Ile Gly Lys Leu Gln Lys Ala Val Ser Glu Glu Cys Ser 185 1190 1195 1200 Tyr Phe Leu Gln Thr Leu Cys Ser Val Leu Gly Glu Tyr Tyr Thr Pro 1205 1200 Tyr The Ser Glu Asn Glu Asp Pro Glu Leu Gln Asp Tyr Arg Tyr Glu 1235 1240 1245 Val Gln Asp Phe Gln Glu Asn Met His Thr Leu Leu Asn Lys Val Thr	1025	5				1030)				103	5				1040
Asp His Leu Pro Ser Val Thr Lys Glu Ser Ser Leu Arg Ala Thr Gln 1075			-		1045	5	_			1050)	_			1055	5
The control of the	GIU	Asn	мет			стх	GLU	GLU			GIN	GIU	GIN			ьeu
1090	Asp	His			Ser	Val	Thr			Ser	Ser	Leu			Thr	Gln
1105		1090)				1095	5				1100)			
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Tyr Ile Ser Glu Asn Glu Asp Pro Glu Leu Gln Asp Tyr Arg Tyr Glu 1235 1240 1245 Val Gln Asp Phe Gln Glu Asn Met His Thr Leu Leu Asn Lys Val Thr	Tyr	Phe	Leu	Gln			Cys	Ser	Val		Gly		Tyr	Tyr		Pro
Tyr Ile Ser Glu Asn Glu Asp Pro Glu Leu Gln Asp Tyr Arg Tyr Glu 1235 1240 1245 Val Gln Asp Phe Gln Glu Asn Met His Thr Leu Leu Asn Lys Val Thr	Ala	Leu	Lys		Glu		Asn	Ala		Asp		Glu	Asn		Gly	
Val Gln Asp Phe Gln Glu Asn Met His Thr Leu Leu Asn Lys Val Thr	Tyr	Ile		Glu		Glu	Asp		Glu		Gln	Asp		Arg		Glu
	Val		Asp		Gln	Glu			His	Thr	Leu			Lys	Val	Thr

Glu Glu Tyr Asn Lys Leu Leu Val Leu Gln Thr Arg Leu Ser Lys Ile 1265 1270 1275 1280
Trp Gly Gln Gln Thr Asp Gly Met Lys Leu Glu Phe Gly Glu Glu Asn 1285 1290 1295 Leu Pro Lys Glu Glu Thr Glu Phe Leu Ser Ile His Ser Gln Met Thr 1300 1305 1310 Asn Leu Glu Asp Ile Asp Val Asn His Lys Ser Lys Leu Ser Ser Leu 1315 1320 1325 Gln Asp Leu Glu Lys Thr Lys Leu Glu Glu Gln Val Gln Glu Leu Glu 1330 1335 1340 Ser Leu Ile Ser Ser Leu Gln Gln Gln Leu Lys Glu Thr Glu Gln Asn 1345 1350 1355 1360 Tyr Glu Ala Glu Ile His Cys Leu Gln Lys Arg Leu Gln Ala Val Ser 1365 1370 1375 Glu Ser Thr Val Pro Pro Ser Leu Pro Val Asp Ser Val Val Ile Thr 1380 1385 1390 Glu Ser Asp Ala Gln Arg Thr Met Tyr Pro Gly Ser Cys Val Lys Lys 1395 1400 1405 Asn Ile Asp Gly Thr Ile Glu Phe Ser Gly Glu Phe Gly Val Lys Glu 1410 1415 1420 Glu Thr Asn Ile Val Lys Leu Leu Glu Lys Gln Tyr Gln Glu Gln Leu 1425 1430 1435 1440 Glu Glu Val Ala Lys Val Ile Val Ser Met Ser Ile Ala Phe Ala $1445 \hspace{3em} 1450 \hspace{3em} 1455$ Gln Gln Thr Glu Leu Ser Arg Ile Ser Gly Gly Lys Glu Asn Thr Ala 1460 1465 1470 Ser Ser Lys Gln Ala His Ala Val Cys Gln Gln Glu Gln His Tyr Phe 1475 1480 1485 Asn Glu Met Lys Leu Ser Gln Asp Gln Ile Gly Phe Gln Thr Phe Glu 1490 1495 1500 Thr Val Asp Val Lys Phe Lys Glu Glu Phe Lys Pro Leu Ser Lys Glu 1505 1510 1515 1520 Leu Gly Glu His Gly Lys Glu Ile Leu Leu Ser Asn Ser Asp Pro His 1525 1530 1535 Asp Ile Pro Glu Ser Lys Asp Cys Val Leu Thr Ile Ser Glu Glu Met 1540 1545 1550 Phe Ser Lys Asp Lys Thr Phe Ile Val Arg Gln Ser Ile His Asp Glu 1555 1560 1565 Ile Ser Val Ser Ser Met Asp Ala Ser Arg Gln Leu Met Leu Asn Glu 1570 1575 1580 Glu Gln Leu Glu Asp Met Arg Gln Glu Leu Val Arg Gln Tyr Gln Glu 1585 1590 1595 1600 His Gln Gln Ala Thr Glu Leu Leu Arg Gln Ala His Met Arg Gln Met 1605 1610 1615 Glu Arg Gln Arg Glu Asp Gln Glu Gln Leu Gln Glu Glu Ile Lys Arg 1620 1625 1630 Leu Asn Arg Gln Leu Ala Gln Arg Ser Ser Ile Asp Asn Glu Asn Leu 1635 1640 1645 Val Ser Glu Arg Glu Arg Val Leu Leu Glu Glu Leu Glu Ala Leu Lys 1650 1655 1660 Gln Leu Ser Leu Ala Gly Arg Glu Lys Leu Cys Cys Glu Leu Arg Asn 1670 1675 1680 Ser Ser Thr Gln Thr Gln Asn Gly Asn Glu Asn Gln Gly Glu Val Glu 1685 1690 Glu Gln Thr Phe Lys Glu Lys Glu Leu Asp Arg Lys Pro Glu Asp Val 1700 1705 Pro Pro Glu Ile Leu Ser Asn Glu Arg Tyr Ala Leu Gln Lys Ala Asn 1720 Asn Arg Leu Leu Lys Ile Leu Leu Glu Val Val Lys Thr Thr Ala Ala

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Ala Ser Val Lys 1780	_	His Glu Glu 1785	His Thr Arg	Val Thr Asp 1790				
Glu Ser Ile Pro 1795	Ser Tyr Ser	Gly Ser Asp 1800	Met Pro Arg	_				
Asn Met Trp Ser 1810	Lys Val Thr		Thr Glu Leu 1820	Ser Gln Arg				
Leu Val Arg Ser 1825				Glu Asn Glu 1840				
Glu Leu Met Leu	Asn Ile Ser 1845	Ser Arg Leu 185		Val Glu Lys 1855				
Leu Leu Glu Ala 1860		Thr Ser Ser 1865	Gln Leu Glu	His Ala Lys 1870				
Val Thr Gln Thr 1875	Glu Leu Met	Arg Glu Ser 1880	Phe Arg Gln 188	-				
Ala Thr Glu Ser 1890	Leu Lys Cys 1895		Leu Arg Glu 1900	Arg Leu His				
Glu Glu Ser Arg 1905	Ala Arg Glu 1910	Gln Leu Ala	Val Glu Leu 1915	Ser Lys Ala 1920				
Glu Gly Val Ile	Asp Gly Tyr 1925	Ala Asp Glu 193		Phe Glu Arg 1935				
Gln Ile Gln Glu 1940		Ile Ile Asp 1945	Arg Leu Glu	Gln Glu Leu 1950				
Leu Cys Ala Ser 1955	Asn Arg Leu	Gln Glu Leu 1960	Glu Ala Glu 196					
Ile Gln Glu Glu 1970	Arg Glu Leu 1975		Gln Lys Glu 1980	Ala Met Lys				
Ala Glu Ala Gly 1985	Pro Val Glu 1990	Gln Gln Leu	Leu Gln Glu 1995	Thr Glu Lys 2000				
Leu Met Lys Glu	2005	201	C	2015				
Asp Asp Leu Gln 2020		Lys Ala Leu 2025	Glu Ile Asp	Val Glu Glu 2030				
Gln Val Ser Arg 2035	Phe Ile Glu	Leu Glu Gln 2040	Glu Lys Asn 204					
Met Asp Leu Arg 2050	2055	5	2060					
Met Arg Lys Phe 2065	Leu Asp Glu 2070	Gln Ala Ile	Asp Arg Glu 2075	His Glu Arg 2080				
Asp Val Phe Gln	Gln Glu Ile 2085	Gln Lys Leu 209		Leu Lys Val 2095				
Val Pro Arg Phe 2100		Ser Glu His 2105	Gln Thr Arg	Glu Val Glu 2110				
Gln Leu Ala Asn 2115	His Leu Lys	Glu Lys Thr 2120	Asp Lys Cys 212					
Leu Leu Ser Lys 2130	Glu Gln Leu 2135		Ile Gln Glu 2140	Arg Asn Glu				
Glu Ile Glu Lys 2145	Leu Glu Phe 2150	Arg Val Arg	Glu Leu Glu 2155	Gln Ala Leu 2160				
Leu Val Ser Ala		Gln Lys Val 2170	Glu Asp Arg					
Gly Ala Val Glu 2180	Ala Lys Pro							
Ala Glu Arg Asp 2195			Lys Glu Ile 220	Thr Asn Leu				

Glu Glu Gln Leu Glu Gln Phe Arg Glu Glu Leu Glu Asn Lys Asn Glu 2210 2215 2220 Glu Val Gln Gln Leu His Met Gln Leu Glu Ile Gln Lys Lys Glu Ser 2230 2235 2240 Thr Thr Arg Leu Glu Glu Leu Glu Glu Asn Lys Leu Phe Lys Asp 2245 2250 2255 Asp Met Glu Lys Leu Gly Leu Ala Ile Lys Glu Ser Asp Ala Met Ser 2260 2265 2270
Thr Gln Asp Gln His Val Leu Phe Gly Lys Phe Ala Gln Ile Ile Gln 2275 2280 2285 Glu Lys Glu Val Glu Ile Asp Gln Leu Asn Glu Gln Val Thr Lys Leu 2290 2295 2300 Gln Gln Leu Lys Ile Thr Thr Asp Asn Lys Val Ile Glu Glu Lys 2310 2315 2320 Asn Glu Leu Ile Arg Asp Leu Glu Thr Gln Ile Glu Cys Leu Met Ser 2325 2330 2335 Asp Gln Glu Cys Val Lys Arg Asn Arg Glu Glu Glu Ile Glu Gln Leu 2340 2345 2350 Asn Glu Val Ile Glu Lys Leu Gln Gln Glu Leu Ala Asn Ile Gly Gln 2355 2360 2365 Lys Thr Ser Met Asn Ala His Ser Leu Ser Glu Glu Ala Asp Ser Leu 2370 . 2375 2380 Lys His Gln Leu Asp Val Val Ile Ala Glu Lys Leu Ala Leu Glu Gln 2385 2390 2395 2400 Gln Val Glu Thr Ala Asn Glu Glu Met Thr Phe Met Lys Asn Val Leu 2405 2410 2415 Lys Glu Thr Asn Phe Lys Met Asn Gln Leu Thr Gln Glu Leu Phe Ser 2420 2425 2430 Leu Lys Arg Glu Arg Glu Ser Val Glu Lys Ile Gln Ser Ile Pro Glu 2435 2440 2445 Asn Ser Val Asn Val Ala Ile Asp His Leu Ser Lys Asp Lys Pro Glu 2450 2455 2460 Leu Glu Val Val Leu Thr Glu Asp Ala Leu Lys Ser Leu Glu Asn Gln 2465 2470 2475 2480 Thr Tyr Phe Lys Ser Phe Glu Glu Asn Gly Lys Gly Ser Ile Ile Asn 2485 2490 2495 Leu Glu Thr Arg Leu Leu Gln Leu Glu Ser Thr Val Ser Ala Lys Asp 2500 2505 2510 Leu Glu Leu Thr Gln Cys Tyr Lys Gln Ile Lys Asp Met Gln Glu Gln 2515 2520 2525 Gly Gln Phe Glu Thr Glu Met Leu Gln Lys Lys Ile Val Asn Leu Gln 2530 2535 2540 Lys Ile Val Glu Glu Lys Val Ala Ala Leu Val Ser Gln Ile Gln Leu Glu Ala Val Gln Glu Tyr Ala Lys Phe Cys Gln Asp Asn Gln Thr 2570 2575 2565 Ile Ser Ser Glu Pro Glu Arg Thr Asn Ile Gln Asn Leu Asn Gln Leu 2580 2585 2590 Arg Glu Asp Glu Leu Gly Ser Asp Ile Ser Ala Leu Thr Leu Arg Ile 2600 Ser Glu Leu Glu Ser Gln Val Val Glu Met His Thr Ser Leu Ile Leu 2615 2620 Glu Lys Glu Gln Val Glu Ile Ala Glu Lys Asn Val Leu Glu Lys Glu 2630 2635 Lys Lys Leu Leu Glu Leu Gln Lys Leu Glu Gly Asn Glu Lys Lys 2645 2650 Gln Arg Glu Lys Glu Lys Lys Arg Ser Pro Gln Asp Val Glu Val Leu 2665 Lys Thr Thr Thr Glu Leu Phe His Ser Asn Glu Glu Ser Gly Phe Phe

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Gln Leu Ser Ser Glu Lys Met Val Val Ala Glu Leu Lys Ser Glu Leu 3155 3160 3165 Ala Gln Thr Lys Leu Glu Leu Glu Thr Thr Leu Lys Ala Gln His Lys 3170 3175 3180 His Leu Lys Glu Leu Glu Ala Phe Arg Leu Glu Val Lys Asp Lys Thr 3185 3190 3195 3200 Asp Glu Val His Leu Leu Asn Asp Thr Leu Ala Ser Glu Gln Lys Lys 3205 3210 3215 Ser Arg Glu Leu Gln Trp Ala Leu Glu Lys Glu Lys Ala Lys Leu Gly 3220 3225 3230 Arg Ser Glu Glu Arg Asp Lys Glu Glu Leu Glu Asp Leu Lys Phe Ser 3235 3240 3245 Leu Glu Ser Gln Lys Gln Arg Asn Leu Gln Leu Asn Leu Leu Leu Glu 3250 3255 3260 Gln Gln Lys Gln Leu Leu Asn Glu Ser Gln Gln Lys Ile Glu Ser Gln **3265 3270 3275 3280** Arg Met Leu Tyr Asp Ala Gln Leu Ser Glu Glu Gln Gly Arg Asn Leu 3285 3290 3295 Glu Leu Gln Val Leu Leu Glu Ser Glu Lys Val Arg Ile Arg Glu Met 3300 3305 3310 Ser Ser Thr Leu Asp Arg Glu Arg Glu Leu His Ala Gln Leu Gln Ser 3315 3320 3325 Ser Asp Gly Thr Gly Gln Ser Arg Pro Pro Leu Pro Ser Glu Asp Leu 3330 3335 3340 Leu Lys Glu Leu Gln Lys Gln Leu Glu Glu Lys His Ser Arg Ile Val **3345 3350 3355 3360** Glu Leu Leu Asn Glu Thr Glu Lys Tyr Lys Leu Asp Ser Leu Gln Thr 3365 3370 3375 Arg Gln Gln Met Glu Lys Asp Arg Gln Val His Arg Lys Thr Leu Gln 3380 3385 3390 Thr Glu Gln Glu Ala Asn Thr Glu Gly Gln Lys Lys Met His Glu Leu 3395 3400 3405 Gln Ser Lys Val Glu Asp Leu Gln Arg Gln Leu Glu Glu Lys Arg Gln 3410 3415 3420 Gln Val Tyr Lys Leu Asp Leu Glu Gly Gln Arg Leu Gln Gly Ile Met 3425 3430 3435 3440 Gln Glu Phe Gln Lys Gln Glu Leu Glu Arg Glu Glu Lys Arg Glu Ser 3445 3450 3455 Arg Arg Ile Leu Tyr Gln Asn Leu Asn Glu Pro Thr Thr Trp Ser Leu 3460 3465 3470 Thr Ser Asp Arg Thr Arg Asn Trp Val Leu Gln Gln Lys Ile Glu Gly 3475 3480 3485 Glu Thr Lys Glu Ser Asn Tyr Ala Lys Leu Ile Glu Met Asn Gly Gly 3490 3495 3500 Gly Thr Gly Cys Asn His Glu Leu Glu Met Ile Arg Gln Lys Leu Gln 3505 3510 3515 3520 Cys Val Ala Ser Lys Leu Gln Val Leu Pro Gln Lys Ala Ser Glu Arg 3525 3530 3535 Leu Gln Phe Glu Thr Ala Asp Asp Glu Asp Phe Ile Trp Val Gln Glu 3540 3545 3550 Asn Ile Asp Glu Ile Ile Leu Gln Leu Gln Lys Leu Thr Gly Gln Gln 3555 3560 3565 Gly Glu Glu Pro Ser Leu Val Ser Pro Ser Thr Ser Cys Gly Ser Leu 3570 3575 3580 Thr Glu Arg Leu Arg Gln Asn Ala Glu Leu Thr Gly His Ile Ser 3595 3590 Gln Leu Thr Glu Glu Lys Asn Asp Leu Arg Asn Met Val Met Lys Leu 3605 3610 Glu Glu Gln Ile Arg Trp Tyr Arg Gln Thr Gly Ala Gly Arg Asp Asn

3620 3625 Ser Ser Arg Phe Ser Leu Asn Gly Gly Ala Asn Ile Glu Ala Ile Ile 3635 3640 3645 Ala Ser Glu Lys Glu Val Trp Asn Arg Glu Lys Leu Thr Leu Gln Lys 3655 3660 Ser Leu Lys Arg Ala Glu Ala Glu Val Tyr Lys Leu Lys Ala Glu Leu 3670 3675 Arg Asn Asp Ser Leu Leu Gln Thr Leu Ser Pro Asp Ser Glu His Val 3685 3690 3695 Thr Leu Lys Arg Ile Tyr Gly Lys Tyr Leu Arg Ala Glu Ser Phe Arg 3700 3705 3710 Lys Ala Leu Ile Tyr Gln Lys Lys Tyr Leu Leu Leu Leu Gly Gly 3715 3720 3725 Phe Gln Glu Cys Glu Asp Ala Thr Leu Ala Leu Leu Ala Arg Met Gly 3735 3740 Gly Gln Pro Ala Phe Thr Asp Leu Glu Val Ile Thr Asn Arg Pro Lys 3745 3750 3755 Gly Phe Thr Arg Phe Arg Ser Ala Val Arg Val Ser Ile Ala Ile Ser 3765 3770 3775 Arg Met Lys Phe Leu Val Arg Arg Trp His Arg Val Thr Gly Ser Val 3780 3785 3790 Ser Ile Asn Ile Asn Arg Asp Gly Phe Gly Leu Asn Gln Gly Ala Glu 3795 3800 3805 Lys Thr Asp Ser Phe Tyr His Ser Ser Gly Gly Leu Glu Leu Tyr Gly 3810 3815 3820 Glu Pro Arg His Thr Thr Tyr Arg Ser Arg Ser Asp Leu Asp Tyr Ile 3825 3830 3835 Arg Ser Pro Leu Pro Phe Gln Asn Arg Tyr Pro Gly Thr Pro Ala Asp 3845 3850 3855 Phe Asn Pro Gly Ser Leu Ala Cys Ser Gln Leu Gln Asn Tyr Asp Pro 3860 3865 3870 Asp Arg Ala Leu Thr Asp Tyr Ile Thr Arg Leu Glu Ala Leu Gln Arg 3875 3880 3885 Arg Leu Gly Thr Ile Gln Ser Gly Ala Leu Ser Leu Thr Thr Ser Trp 3890 3895 3900 Gln His His Ser Ala Arg Pro Thr Ala Pro Leu Phe Phe Glu Ile Leu 3905 3910 3915 Ser His Ser Leu Gly 3925

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	690					695					700	Lys			-
Leu	Gln	Gln	Ser	Leu	Val	Asn	Ser	Lys	Ser	Glu	Glu	Met	Thr	Leu	Gln

710 705 715 Ile Asn Glu Leu Gln Lys Glu Ile Glu Ile Leu Arg Gln Glu Glu Lys 725 730 Glu Lys Gly Thr Leu Glu Gln Glu Val Gln Glu Leu Gln Leu Lys Thr 745 Glu Leu Leu Glu Lys Gln Met Lys Glu Lys Glu Asn Asp Leu Gln Glu 760 Lys Phe Ala Gln Leu Glu Ala Glu Asn Ser Ile Leu Lys Asp Glu Lys 775 Lys Thr Leu Glu Asp Met Leu Lys Ile His Thr Pro Val Ser Gln Glu 790 795 Glu Arg Leu Ile Phe Leu Asp Ser Ile Lys Ser Lys Ser Lys Asp Ser 805 810 Val Trp Glu Lys Glu Ile Glu Ile Leu Ile Glu Glu Asn Glu Asp Leu 825 Lys Gln Gln Cys Ile Gln Leu Asn Glu Glu Ile Glu Lys Gln Arg Asn 840 Thr Phe Ser Phe Ala Glu Lys Asn Phe Glu Val Asn Tyr Gln Glu Leu 855 860 Gln Glu Glu Tyr Ala Cys Leu Leu Lys Val Lys Asp Asp Leu Glu Asp 865 870 875 Ser Lys Asn Lys Gln Glu Leu Glu Tyr Lys Ser Lys Leu Lys Ala Leu · 885 890 Asn Glu Glu Leu His Leu Gln Arg Ile Asn Pro Thr Thr Val Lys Met 900 905 Lys Ser Ser Val Phe Asp Glu Asp Lys Thr Phe Val Ala Glu Thr Leu 915 920 925 Glu Met Gly Glu Val Val Glu Lys Asp Thr Thr Glu Leu Met Glu Lys 935 940 Leu Glu Val Thr Lys Arg Glu Lys Leu Glu Leu Ser Gln Arg Leu Ser 950 955 Asp Leu Ser Glu Gln Leu Lys Gln Lys His Gly Glu Ile Ser Phe Leu 965 970 Asn Glu Glu Val Lys Ser Leu Lys Gln Glu Lys Glu Gln Val Ser Leu 980 985 Arg Cys Arg Glu Leu Glu Ile Ile Ile Asn His Asn Arg Ala Glu Asn 995 1000 1005 Val Gln Ser Cys Asp Thr Gln Val Ser Ser Leu Leu Asp Gly Val Val 1020 1010 1015 Thr Met Thr Ser Arg Gly Ala Glu Gly Ser Val Ser Lys Val Asn Lys 1030 1035 1040 Ser Phe Gly Glu Glu Ser Lys Ile Met Val Glu Asp Lys Val Ser Phe 1045 1050 Glu Asn Met Thr Val Gly Glu Glu Ser Lys Gln Glu Gln Leu Ile Leu 1060 1065 1070 Asp His Leu Pro Ser Val Thr Lys Glu Ser Ser Leu Arg Ala Thr Gln 1075 1080 1085 Pro Ser Glu Asn Asp Lys Leu Gln Lys Glu Leu Asn Val Leu Lys Ser 1090 1095 1100 Glu Gln Asn Asp Leu Arg Leu Gln Met Glu Ala Gln Arg Ile Cys Leu 1105 1110 1115 1120 Ser Leu Val Tyr Ser Thr His Val Asp Gln Val Arg Glu Tyr Met Glu 1125 1130 1135 Asn Glu Lys Asp Lys Ala Leu Cys Ser Leu Lys Glu Glu Leu Ile Phe 1140 1145 1150 Ala Gln Glu Glu Lys Ile Lys Glu Leu Gln Lys Ile His Gln Leu Glu 1155 1160 1165 Leu Gln Thr Met Lys Thr Gln Glu Thr Gly Asp Glu Gly Lys Pro Leu 1170 1175

His Leu Leu Ile Gly Lys Leu Gln Lys Ala Val Ser Glu Glu Cys Ser 1205 1210 1215 Ala Leu Lys Cys Glu Val Asn Ala Glu Asp Lys Glu Asn Ser Gly Asp 1220 1225 1230 Tyr Ile Ser Glu Asn Glu Asp Pro Glu Leu Gln Asp Tyr Arg Tyr Glu 1235 1240 1245 Val Gln Asp Phe Gln Glu Asn Met His Thr Leu Leu Asn Lys Val Thr 1250 1255 1260 Glu Glu Tyr Asn Lys Leu Leu Val Leu Gln Thr Arg Leu Ser Lys Ile 1265 1270 1275 1280 Trp Gly Gln Gln Thr Asp Gly Met Lys Leu Glu Phe Gly Glu Glu Asn 1285 1290 1295 Leu Pro Lys Glu Glu Thr Glu Phe Leu Ser Ile His Ser Gln Met Thr 1300 1305 1310 Asn Leu Glu Asp Ile Asp Val Asn His Lys Ser Lys Leu Ser Ser Leu 1315 1320 1325 Gln Asp Leu Glu Lys Thr Lys Leu Glu Glu Gln Val Gln Glu Leu Glu 1330 1335 1340 Ser Leu Ile Ser Ser Leu Gln Gln Gln Leu Lys Glu Thr Glu Gln Asn 1345 1350 1355 1360 Tyr Glu Ala Glu Ile His Cys Leu Gln Lys Arg Leu Gln Ala Val Ser 1365 1370 1375 Glu Ser Thr Val Pro Pro Ser Leu Pro Val Asp Ser Val Val Ile Thr 1380 1385 1390 Glu Ser Asp Ala Gln Arg Thr Met Tyr Pro Gly Ser Cys Val Lys 1395 1400 1405 Asn Ile Asp Gly Thr Ile Glu Phe Ser Gly Glu Phe Gly Val Lys Glu 1410 1415 1420 Glu Thr Asn Ile Val Lys Leu Leu Glu Lys Gln Tyr Gln Glu Gln Leu 1425 1430 1435 1440 Glu Glu Glu Val Ala Lys Val Ile Val Ser Met Ser Ile Ala Phe Ala 1445 1450 1455 Gln Gln Thr Glu Leu Ser Arg Ile Ser Gly Gly Lys Glu Asn Thr Ala 1460 1465 1470 Ser Ser Lys Gln Ala His Ala Val Cys Gln Gln Glu Gln His Tyr Phe 1475 1480 1485 Asn Glu Met Lys Leu Ser Gln Asp Gln Ile Gly Phe Gln Thr Phe Glu 1490 1495 1500
Thr Val Asp Val Lys Phe Lys Glu Glu Phe Lys Pro Leu Ser Lys Glu **1505 1510 1515 1520** Leu Gly Glu His Gly Lys Glu Ile Leu Leu Ser Asn Ser Asp Pro His
 1525
 1530

 1535
 Asp Ile Pro Glu Ser Lys Asp Cys Val Leu Thr Ile Ser Glu Glu Met $1540 \hspace{1.5cm} 1545 \hspace{1.5cm} 1550$ Phe Ser Lys Asp Lys Thr Phe Ile Val Arg Gln Ser Ile His Asp Glu 1555 1560 1565 Ile Ser Val Ser Ser Met Asp Ala Ser Arg Gln Leu Met Leu Asn Glu 1570 1575 1580 $^{\circ}$ Glu Gln Leu Glu Asp Met Arg Gln Glu Leu Val Arg Gln Tyr Gln Glu 1585 1590 1595 . 1600 His Gln Gln Ala Thr Glu Leu Leu Arg Gln Ala His Met Arg Gln Met 1605 1610 Glu Arg Gln Arg Glu Asp Gln Glu Gln Leu Gln Glu Glu Ile Lys Arg 1620 1625 1630 Leu Asn Arg Gln Leu Ala Gln Arg Ser Ser Ile Asp Asn Glu Asn Leu 1635 1640 1645 Val Ser Glu Arg Glu Arg Val Leu Leu Glu Glu Leu Glu Ala Leu Lys

1650 1655 1660 Gln Leu Ser Leu Ala Gly Arg Glu Lys Leu Cys Cys Glu Leu Arg Asn 1670 1675 1680 Ser Ser Thr Gln Thr Gln Asn Gly Asn Glu Asn Gln Gly Glu Val Glu 1685 1690 1695 Glu Gln Thr Phe Lys Glu Lys Glu Leu Asp Arg Lys Pro Glu Asp Val 1705 1710 Pro Pro Glu Ile Leu Ser Asn Glu Arg Tyr Ala Leu Gln Lys Ala Asn 1715 1720 1725 Asn Arg Leu Leu Lys Ile Leu Leu Glu Val Val Lys Thr Thr Ala Ala 1730 1735 1740 Val Glu Glu Thr Ile Gly Arg His Val Leu Gly Ile Leu Asp Arg Ser 1745 1750 1755 1760 Ser Lys Ser Gln Ser Ser Ala Ser Leu Ile Trp Arg Ser Glu Ala Glu 1765 1770 1775 Ala Ser Val Lys Ser Cys Val His Glu Glu His Thr Arg Val Thr Asp 1780 1785 1790 Glu Ser Ile Pro Ser Tyr Ser Gly Ser Asp Met Pro Arg Asn Asp Ile 1795 1800 1805 Asn Met Trp Ser Lys Val Thr Glu Glu Gly Thr Glu Leu Ser Gln Arg 1810 1815 1820 Leu Val Arg Ser Gly Phe Ala Gly Thr Glu Ile Asp Pro Glu Asn Glu 1825 1830 1835 1840 Glu Leu Met Leu Asn Ile Ser Ser Arg Leu Gln Ala Ala Val Glu Lys 1845 1850 1855 Leu Leu Glu Ala Ile Ser Glu Thr Ser Ser Gln Leu Glu His Ala Lys 1860 1865 1870 Val Thr Gln Thr Glu Leu Met Arg Glu Ser Phe Arg Gln Lys Gln Glu 1875 1880 1885 Ala Thr Glu Ser Leu Lys Cys Gln Glu Glu Leu Arg Glu Arg Leu His 1890 1895 1900 Glu Glu Ser Arg Ala Arg Glu Gln Leu Ala Val Glu Leu Ser Lys Ala 1905 1910 1915 1920 Glu Gly Val Ile Asp Gly Tyr Ala Asp Glu Lys Thr Leu Phe Glu Arg 1925 1930 1935 Gln Ile Gln Glu Lys Thr Asp Ile Ile Asp Arg Leu Glu Gln Glu Leu 1940 1945 1950 Leu Cys Ala Ser Asn Arg Leu Gln Glu Leu Glu Ala Glu Gln Gln 1955 1960 1965 Ile Gln Glu Glu Arg Glu Leu Leu Ser Arg Gln Lys Glu Ala Met Lys 1970 1975 1980 Ala Glu Ala Gly Pro Val Glu Gln Gln Leu Leu Gln Glu Thr Glu Lys 1985 1990 1995 Leu Met Lys Glu Lys Leu Glu Val Gln Cys Gln Ala Glu Lys Val Arg 2005 2010 Asp Asp Leu Gln Lys Gln Val Lys Ala Leu Glu Ile Asp Val Glu Glu 2020 2025 2030 Gln Val Ser Arg Phe Ile Glu Leu Glu Gln Glu Lys Asn Thr Glu Leu 2035 2040 2045 Met Asp Leu Arg Gln Gln Asn Gln Ala Leu Glu Lys Gln Leu Glu Lys 2050 2055 2060 Met Arg Lys Phe Leu Asp Glu Gln Ala Ile Asp Arg Glu His Glu Arg 2065 2070 2075 2080 Asp Val Phe Gln Glu Glu Gln Lys Leu Glu Gln Gln Leu Lys Val 2085 2090 2095 Val Pro Arg Phe Gln Pro Ile Ser Glu His Gln Thr Arg Glu Val Glu 2100 2105 2110 Gln Leu Ala Asn His Leu Lys Glu Lys Thr Asp Lys Cys Ser Glu Leu 2115 2120 2125

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Leu Ser Lys Glu Gln Leu Gln Arg Asp Ile Gln Glu Arg Asn Glu 2130 2135 2140 Glu Ile Glu Lys Leu Glu Phe Arg Val Arg Glu Leu Glu Gln Ala Leu 2145 2150 2155 Leu Val Glu Asp Arg Lys His Phe Gly Ala Val Glu Ala Lys Pro Glu 2165 2170 2175 Leu Ser Leu Glu Val Gln Leu Gln Ala Glu Arg Asp Ala Ile Asp Arg 2180 2185 2190 Lys Glu Lys Glu Ile Thr Asn Leu Glu Glu Gln Leu Glu Gln Phe Arg 2195 2200 2205 Glu Glu Leu Glu Asn Lys Asn Glu Glu Val Gln Gln Leu His Met Gln 2210 2215 2220 Leu Glu Ile Gln Lys Lys Glu Ser Thr Thr Arg Leu Gln Glu Leu Glu 2225 2230 2235 2240 Gln Glu Asn Lys Leu Phe Lys Asp Met Glu Lys Leu Gly Leu Ala 2245 2250 2255 Ile Lys Glu Ser Asp Ala Met Ser Thr Gln Asp Gln His Val Leu Phe 2260 2265 2270 Gly Lys Phe Ala Gln Ile Ile Gln Glu Lys Glu Val Glu Ile Asp Gln 2275 2280 2285 Leu Asn Glu Gln Val Thr Lys Leu Gln Gln Gln Leu Lys Ile Thr Thr 2290 2295 2300 Asp Asn Lys Val Ile Glu Glu Lys Asn Glu Leu Ile Arg Asp Leu Glu 2305 2310 2315 Thr Gln Ile Glu Cys Leu Met Ser Asp Gln Glu Cys Val Lys Arg Asn 2325 2330 2335 Arg Glu Glu Glu Ile Glu Gln Leu Asn Glu Val Ile Glu Lys Leu Gln 2340 2345 2350 Gln Glu Leu Ala Asn Ile Gly Gln Lys Thr Ser Met Asn Ala His Ser 2355 2360 2365 Leu Ser Glu Glu Ala Asp Ser Leu Lys His Gln Leu Asp Val Val Ile 2370 2375 2380 Ala Glu Lys Leu Ala Leu Glu Gln Gln Val Glu Thr Ala Asn Glu Glu 2385 2390 2395 Met Thr Phe Met Lys Asn Val Leu Lys Glu Thr Asn Phe Lys Met Asn 2405 2410 2415 Gln Leu Thr Gln Glu Leu Phe Ser Leu Lys Arg Glu Arg Glu Ser Val 2420 2425 Glu Lys Ile Gln Ser Ile Pro Glu Asn Ser Val Asn Val Ala Ile Asp 2435 2440 2445 His Leu Ser Lys Asp Lys Pro Glu Leu Glu Val Val Leu Thr Glu Asp 2450 2455 2460 Ala Leu Lys Ser Leu Glu Asn Gln Thr Tyr Phe Lys Ser Phe Glu Glu 2465 2470 2475 Asn Gly Lys Gly Ser Ile Ile Asn Leu Glu Thr Arg Leu Leu Gln Leu 2485 2490 Glu Ser Thr Val Ser Ala Lys Asp Leu Glu Leu Thr Gln Cys Tyr Lys 2500 2505 Gln Ile Lys Asp Met Gln Glu Gln Gly Gln Phe Glu Thr Glu Met Leu 2520 Gln Lys Lys Ile Val Asn Leu Gln Lys Ile Val Glu Glu Lys Val Ala 2535 2540 Ala Ala Leu Val Ser Gln Ile Gln Leu Glu Ala Val Gln Glu Tyr Ala 2550 2555 Lys Phe Cys Gln Asp Asn Gln Thr Ile Ser Ser Glu Pro Glu Arg Thr 2565 2570 2575 Asn Ile Gln Asn Leu Asn Gln Leu Arg Glu Asp Glu Leu Gly Ser Asp 2585 Ile Ser Ala Leu Thr Leu Arg Ile Ser Glu Leu Glu Ser Gln Val Val

47

		2595	5				2600	1				2605	5		
GIII	Met			Ser	Leu	Tle			Lvs	Glu	Gln	Val		Tle	Ala
02.0	2610			~ 01		2615		014	шуо	014	2620		0± u	110	1114
Glu			Val	Len	Glu			Lvs	Lvs	T ₁ e11		Glu	Len	Gln	Lvs
2625			,	ou	2630		014	my o	טעב	2635		O.L.a	шоц	0111	2640
		Glu	Glv	Asn			Tivs	Gln	Ara			Glu	T.vs	T.375	
шοα	200	Ond	O _T y	2645		ی پرید	٠,٧٥	02.11	2650		ى رىد	01.4	ى رى	2655	-
Sar	Dro	Gln	Aen			7757	T.011	T.376			Thr	Glu	T.O.		
Der	LLO	OTII	2660		GIU	vaı	шеα	2665		1111	TIIT	Giu	2670		117.2
Sor	λαη	Glu			Clar	Dho	Dho			Lou	Cla	Ala			7\ 1 ~
Ser	ASII	2675		Ser	GTÀ	FILE	2680		Gru	пеп	Gru	2685		ALG	Ата
C1.	C 0 20			The se	T	7\ 7\ ~			7\ 7\ -	C 0 **	III			T	71 -
GIU	2690		Ата	TIIT	пур	2695		ьец	Ата	ser	2700	Lys	GIU	пуѕ	AId
C1			C1~	C1	C1			77m 7	T	C1			Mak	(II) be see	0
270	-	пеп	GTII	GIU			ьеи	Val	туз			Asn	мес	TIIT	
		Tura	7\ 0.70	Т олг	2710		۲7 - ۲	7\~~	7\ ~~	2715		70.71	C3	ח ז ת	2720
пеα	GTII	пуѕ	Asp			GTII	val	Arg	2730		ьеα	Ala	GIU		_
Clu	T 110	T 011	202	2725		C1.,	T	C1			Пb м	<i>C</i> 1	77- J	2735	
Gru	пуѕ	лец	2740		шец	GIU	туг	2745		GIU	TIIT	Glu	2750		GIU
Cox	T ***	T			Mot	Dha	C1			Dage	Tla	T			T
ser	туѕ			Cys	Met	Pne			ьeu	Pro	тте	Lys		ser	гÀг
0	T7 -	2755		Q1	m1	70	2760		T	т	~1.	2765		G	70
ser			ser	GIN	Thr		_	Thr	ьeu	ьys		Ser	ser	Ser	Asn
Q7	2770		6 7	77 71 -	~	2775		70	70 J	a i	2780		~ 7	-	T
		Pro	GIN	тте			ьуѕ	Asn	Ата			Gln	тте	Asn	
278		C1	C	0	2790		C1	τ7 7	m1	2795		~ 7 -	0	C1	2800
GTII	ser	GIU	Cys	2805		GIU	GIU	val	2810		тте	Ile	ser		
Thr	C1.11	T 110	тло			Mot	Cln	Clu			7\1_0	- בע	C1	2815	
TIIT	GIU	туя	2820		ту	мес	GTII	2825		птѕ	Ата	Ala			ьеи
Λen	Mot	Clu			піс	Tlo	Cor			C1	Thr	Leu	2830		C1,,
ASP	Mec	2835		ALG	птэ	тте	2840		TIIT	GIU	TIIT	2845	_	Arg	GIU
Пie	Trans			U = 1	Gln	T.011			Glu	Glu	Cve	Gly		T. 011	Tare
1143	2850		пла	var	GLII	285		цуз	Gru	GLU	2860		TIIT	шеи	пуs
АТа			Gln	Cvs	T.e.11			Tays	G711	Glv		Ser	Tla	Pro	Glu
286		110	0_11	CYD	2870		OCI	пуо	OIU	2875		DCT	110	110	2880
		His	Ser	Asn			Gln	Thr	Ara			Cys	Ser	Ser	
	1124	1110	001	2885		- <u>y</u> -	0111	±11±	2890		110	Cyb	DCI	2895	
Ser	Glv	Ser	Asp			Gln	Glv	Tle			Thr	His	Ser		
	0_1	~~~	2900			J	<u></u>	2905				*****	2910		وسرح
Phe	Asp	Tle			Glu	Glv	Ara			Glu	Ser	Glu			Thr
		2915	5				2920)				2925	5		
Asp	Ser	Phe	Pro	Lvs	Lvs	Tle	Lvs	Glv	Leu	Leu	Ara	Ala	Val	His	Asn
	2930			-1-	-1-	2935		1	ou		2940				-1011
Glu			Gln	Val	Leu			Thr	Glu	Ser		Tyr	Ser	Asp	Glv
294					2950				0	2955		- 3		1101	2960
		His	Ser	Ile			Val	Ser	Glu			Leu	Glu	Glu	-
				2965					2970					2975	_
Lvs	Ala	Tvr	Ile			Ile	Ser	Ser			Asp	Leu	Ile		
		2	2980					2985					2990		-2-
Met	Gln	Leu			Glu	Ala	Glu			Asp	Ser	Ser			His
		299		5			3000		-1-	ي		3005			
Glu	Ser			Asp	Tro	Ara			Ten	Len	T.en	Ala		Gln	Gln
	3010			E		3015					3020		u	·	
Val			Glu	Glu	Ara			T.e.11	T.A.I	Δla		Phe	Ara	Thr	Glu
302		<u> </u>	<u> </u>	~~ u	3030		٧ал	Lou	سات	3035		r 11G	411.9	****	3040
		Δla	Leu	Glv			Asp	Δla	Val			Leu	Asn	Cvs	
u		1 1 L U		3045			, rob	4 1 L U	3050		שטע	ساتىد	11 ت	3055	
Glu	Gln	Ara	Ile			Gln	Gl v	Val			Gln	Ala	Ala		
	GIII	112.9	3060					3065		-4			3070		Ozu

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Cys Leu Gln Lys Ala Asp Arg Arg Ser Leu Leu Ser Glu Ile Gln Ala 3075 3080 3085 Leu His Ala Gln Met Asn Gly Arg Lys Ile Thr Leu Lys Arg Glu Gln 3090 3095 3100 Glu Ser Glu Lys Pro Ser Gln Glu Leu Leu Glu Tyr Asn Ile Gln Gln 3110 3115 3120 Lys Gln Ser Gln Met Leu Glu Met Gln Val Glu Leu Ser Ser Met Lys 3125 3130 3135 Asp Arg Ala Thr Glu Leu Gln Glu Gln Leu Ser Ser Glu Lys Met Val 3140 3145 3150 Val Ala Glu Leu Lys Ser Glu Leu Ala Gln Thr Lys Leu Glu Leu Glu 3155 3160 3165 Thr Thr Leu Lys Ala Gln His Lys His Leu Lys Glu Leu Glu Ala Phe 3170 3175 3180 Arg Leu Glu Val Lys Asp Lys Thr Asp Glu Val His Leu Leu Asn Asp 3185 3190 3195 3200 Thr Leu Ala Ser Glu Gln Lys Lys Ser Arg Glu Leu Gln Trp Ala Leu 3205 3210 3215 Glu Lys Glu Lys Ala Lys Leu Gly Arg Ser Glu Glu Arg Asp Lys Glu 3220 3225 3230 Glu Leu Glu Asp Leu Lys Phe Ser Leu Glu Ser Gln Lys Gln Arg Asn 3235 3240 3245 Leu Gln Leu Asn Leu Leu Glu Gln Gln Lys Gln Leu Leu Asn Glu 3250 3255 3260 Ser Gln Gln Lys Ile Glu Ser Gln Arg Met Leu Tyr Asp Ala Gln Leu **3265 3270 3275 3280** Ser Glu Glu Gln Gly Arg Asn Leu Glu Leu Gln Val Leu Leu Glu Ser 3285 3290 3295 Glu Lys Val Arg Ile Arg Glu Met Ser Ser Thr Leu Asp Arg Glu Arg 3300 3305 3310 Glu Leu His Ala Gln Leu Gln Ser Ser Asp Gly Thr Gly Gln Ser Arg 3315 3320 3325 Pro Pro Leu Pro Ser Glu Asp Leu Leu Lys Glu Leu Gln Lys Gln Leu 3330 3335 3340 Glu Glu Lys His Ser Arg Ile Val Glu Leu Leu Asn Glu Thr Glu Lys **3345 3350 3355 3360** Tyr Lys Leu Asp Ser Leu Gln Thr Arg Gln Gln Met Glu Lys Asp Arg 3365 3370 3375 Gln Val His Arg Lys Thr Leu Gln Thr Glu Gln Glu Ala Asn Thr Glu 3380 3385 3390 Gly Gln Lys Lys Met His Glu Leu Gln Ser Lys Val Glu Asp Leu Gln 3395 3400 3405 Arg Gln Leu Glu Glu Lys Arg Gln Gln Val Tyr Lys Leu Asp Leu Glu 3410 3415 3420 Gly Gln Arg Leu Gln Gly Ile Met Gln Glu Phe Gln Lys Gln Glu Leu 3425 3430 3435 Glu Arq Glu Glu Lys Arg Glu Ser Arg Arg Ile Leu Tyr Gln Asn Leu 3445 3450 Asn Glu Pro Thr Thr Trp Ser Leu Thr Ser Asp Arg Thr Arg Asn Trp 3465 Val Leu Gln Gln Lys Ile Glu Gly Glu Thr Lys Glu Ser Asn Tyr Ala 3480 Lys Leu Ile Glu Met Asn Gly Gly Gly Thr Gly Cys Asn His Glu Leu 3495 3500 Glu Met Ile Arg Gln Lys Leu Gln Cys Val Ala Ser Lys Leu Gln Val 3510 3515 Leu Pro Gln Lys Ala Ser Glu Arg Leu Gln Phe Glu Thr Ala Asp Asp 3530 Glu Asp Phe Ile Trp Val Gln Glu Asn Ile Asp Glu Ile Ile Leu Gln

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<211> 2850

<212> DNA

<213> Homo sapiens

<400> 9

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3895

Ala Pro Leu Phe Phe Glu Ile Leu Ser His Ser Leu Gly

3910

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Asn Trp His Asp Lys Gly Gln Gln Tyr Arg Asn Trp Phe Leu Lys Glu
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Phe Pro Arg Leu Lys Ser Lys Leu Glu Asp Asn Ile Arg Arg Leu Arg
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Ala Leu Ala Asp Gly Val Gln Lys Val His Lys Gly Thr Thr Ile Ala
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Asn Val Val Ser Gly Ser Leu Ser Ile Ser Ser Gly Ile Leu Thr Leu
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Leu Val Tyr Glu Ser Lys His Leu His Glu Gly Ala Lys Ser Glu Thr
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<400> 11

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<211> 3004

<212> DNA

<213> Homo sapiens

WO 02/101075 PCT/US02/18638

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<211> 414
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<212> PRT

<213> Homo sapiens

<400> 12

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<211> 2298
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<400> 13

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<212> DNA

<213> Homo sapiens

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<211> 331

<212> PRT

<213> Homo sapiens

<400> 14

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Arg Ala Ile Arg Gln Ala Arg Ala Arg Ala Arg Leu Pro Val Thr Thr
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Trp Arg Ile Ser Ala Gly Ser Gly Gln Ala Glu Arg Thr Ile Ala
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                                    250
Gly Thr Thr Arg Ala Val Ser Arg Gly Ala Arg Ile Leu Ser Ala Thr
                                265
                                                    270
Thr Ser Gly Ile Phe Leu Ala Leu Asp Val Val Asn Leu Val Tyr Glu
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                            280
                                                285
Ser Lys His Leu His Glu Gly Ala Lys Ser Ala Ser Ala Glu Glu Leu
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<213> Homo sapiens

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<210> 16

<211> 265

<212> PRT

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<400> 16

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Gly Gly His Ile Asn Pro Ala Ile Thr Leu Ala Leu Leu Val Gly Asn
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Gln Ile Ser Leu Leu Arg Ala Phe Phe Tyr Val Ala Ala Gln Leu Val
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Ala Arg Gly Asn Leu Ala Val Asn Ala Leu Asn Asn Asn Thr Thr Gln
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Gly Gln Ala Met Val Val Glu Leu Ile Leu Thr Phe Gln Leu Ala Leu
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Cys Ile Phe Ala Ser Thr Asp Ser Arg Arg Thr Ser Pro Val Gly Ser
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Pro Ala Leu Ser Ile Gly Leu Ser Val Thr Leu Gly His Leu Val Gly
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<210> 17 <211> 1258

<212> DNA

<213> Homo sapiens

<400> 17

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Asn Ser Glu Ala Cys Arg Asp Gly Leu Arg Ala Val Met Glu Cys Arg
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Asn Val Thr His Leu Leu Gln Gln Glu Leu Thr Glu Ala Gln Lys Gly
                   70
                                       75
Phe Gln Asp Val Glu Ala Gln Ala Ala Thr Cys Asn His Thr Val Met
Ala Leu Met Ala Ser Leu Asp Ala Glu Lys Ala Gln Gly Gln Lys Lys
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Glu Arg Gln Asp Pro Gly Ser Ala Pro Ser Pro Leu Ser Leu Leu His
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Pro Gly Val Ala Ala Lys Gly Lys His Ala Ser Glu Lys Arg His Lys
                        135
Cys Pro Tyr Ser Gly Cys Gly Lys Val Tyr Gly Lys Ser Ser His Leu
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                                        155
Lys Ala His Tyr Arg Val His Thr Gly Glu Arg Pro Phe Pro Cys Thr
                165
                                    170
Trp Pro Asp Cys Leu Lys Lys Phe Ser Arg Ser Asp Glu Leu Thr Arg
                                185
            180
                                                     190
His Tyr Arg Thr His Thr Gly Glu Lys Gln Phe Arg Cys Pro Leu Cys
                            200
                                                 205
Glu Lys Arg Phe Met Arg Ser Asp His Leu Thr Lys His Ala Arg Arg
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His Thr Glu Phe His Pro Ser Met Ile Lys Arg Ser Lys Lys Ala Leu
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Ala Asn Ala Leu
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<211> 1304

<212> DNA

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<211> 232

<212> PRT

<213> Homo sapiens

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PCT/US02/18638

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Ala Thr Thr Ala Tyr Phe Leu Tyr Gln Gln Gln Gly Arg Leu Asp Lys
                    70
                                        75
Leu Thr Val Thr Ser Gln Asn Leu Gln Leu Glu Asn Leu Arg Met Lys
Leu Pro Lys Pro Pro Lys Pro Val Ser Lys Met Arg Met Ala Thr Pro
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Leu Leu Met Gln Ala Leu Pro Met Gly Ala Leu Pro Gln Gly Pro Met
                            120
                                                125
Gln Asn Ala Thr Lys Tyr Gly Asn Met Thr Glu Asp His Val Met His
                        135
                                            140
Leu Leu Gln Asn Ala Asp Pro Leu Lys Val Tyr Pro Pro Leu Lys Gly
                    150
                                        155
Ser Phe Pro Glu Asn Leu Arg His Leu Lys Asn Thr Met Glu Thr Ile
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                165
                                                        175
Asp Trp Lys Val Phe Glu Ser Trp Met His His Trp Leu Leu Phe Glu
            180
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Met Ser Arg His Ser Leu Glu Gln Lys Pro Thr Asp Ala Pro Pro Lys
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<213> Homo sapiens

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<213> Homo sapiens

<400> 26

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63

Gln Val Cys Ser Ile Leu Trp Ser Pro His Tyr Lys Glu Leu Ile Ser 405 410 Gly His Gly Phe Ala Gln Asn Gln Leu Val Ile Trp Lys Tyr Pro Thr 420 425 Met Ala Lys Val Ala Glu Leu Lys Gly His Thr Ser Arg Val Leu Ser 440 Leu Thr Met Ser Pro Asp Gly Ala Thr Val Ala Ser Ala Ala Asp 455 Glu Thr Leu Arg Leu Trp Arg Cys Phe Glu Leu Asp Pro Ala Arg Arg 470 475 Arg Glu Arg Glu Lys Ala Ser Ala Ala Lys Ser Ser Leu Ile His Gln 490 Gly Ile Arg

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Leu Lys Asp Arg Thr Gly Phe Ala Val Ile His Asp Ala Ala Arg Ala
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Gly Phe Leu Asp Thr Leu Gln Thr Leu Leu Glu Phe Gln Ala Asp Val
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<212> PRT

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245

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370

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375

380

WO 02/101075

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Gly	Pro	Ala 1075		Pro	Val	Gly	Pro 1080		Gly	Ala	Arg	Gly 108		Ala	Gly
Pro	Gln 1090		Pro	Arg	Gly	Asp 1095	Lys		Glu	Thr	Gly 1100	Glu		Gly	Asp
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Leu	Pro	Gln	Pro	Pro 1205		Glu	Lys	Ala	His 121	Asp		Gly	Arg	Tyr 1215	Tyr
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Thr	Thr	Leu 1235	Lys	Ser	Leu	Ser	Gln 1240	Gln		Glu	Asn	Ile 1245	Arg		Pro
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Glu	Thr	Cys	Val 1300	Tyr		Thr	Gln	Pro 1305	Ser		Ala	Gln	Lys 1310	Asn	
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Gly 625	Val	Val	Gly	Ala	Val 630	Gly	Thr	Ala	Gly	Pro 635	Ser	Gly	Pro	Ser	Gly 640
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705					710	Pro				715					720
				725		Gly			730			_	•	735	_
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Lys	Pro 210	Gly	Gly	Pro	Gly	Leu 215	Pro	Gly	Gln	Pro	Gly 220	Pro	Lys	Gly	Asp
Arg 225	Gly	Pro	Lys	Gly	Leu 230	Pro	Gly	Pro	Gln	Gly 235	Leu	Arg	Gly	Pro	Lys 240
Gly	Asp	Lys	Gly	Phe 245	Gly	Met	Pro	Gly	Ala 250	Pro	Gly	Val	Lys	Gly 255	Pro
Pro	Gly	Met	His 260	Gly	Leu	Pro	Gly	Pro 265	Val	Gly	Leu	Pro	Gly 270	Val	Gly
		275					Pro 280					285			
	290					295	Gly				300				
Gly 305	Val	Gln	Gly	Pro	Pro 310	Gly	Ile	Pro	Gly	Ile 315	Gly	Lys	Pro	Gly	Gln 320
	_			325			Gly		330	_	_	_	_	335	
			340				Ala	345					350		
		355					Gly 360					365	_		
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385					390		Pro			395					400
				405			Gly		410			_	-	415	_
			420				Pro	425					430		
		435					Pro 440					445			
	450					455	Gly				460				
465					470		Leu			475		_			480
				485			Pro		490					495	
	_		500			_	Gly	505		_			510		
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Asn Val Trp Val Ala Leu Phe Lys Asn Asn Glu Pro Val Met Tyr Thr
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Tyr Asp Glu Tyr Lys Lys Gly Phe Leu Asp Gln Ala Ser Gly Ser Ala
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Val Leu Leu Arg Pro Gly Asp Arg Val Phe Leu Gln Met Pro Ser
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Asn Leu Glu Asn Ser Thr Tyr Asp Leu Tyr Thr Ile Pro Lys Asp Ala 390 395 Asp Ser Gln Asn Pro Asp Ala Pro Glu Gly Lys Arg Ser Ser Gly Leu 405 410 Thr Ala Val Trp Val Ala Arg Asn Arg Phe Ala Val Leu Asp Arg Met 420 425 His Ser Leu Leu Ile Lys Asn Leu Lys Asn Glu Ile Thr Lys Lys Val 440 Gln Val Pro Asn Cys Asp Glu Ile Phe Tyr Ala Gly Thr Gly Asn Leu 455 Leu Leu Arg Asp Ala Asp Ser Ile Thr Leu Phe Asp Val Gln Gln Lys 470 475 Arg Thr Leu Ala Ser Val Lys Ile Ser Lys Val Lys Tyr Val Ile Trp 490 485 Ser Ala Asp Met Ser His Val Ala Leu Leu Ala Lys His Ala Ile Val 505 Ile Cys Asn Arg Lys Leu Asp Ala Leu Cys Asn Ile His Glu Asn Ile 520 515 525 Arg Val Lys Ser Gly Ala Trp Asp Glu Ser Gly Val Phe Ile Tyr Thr 540 535 Thr Ser Asn His Ile Lys Tyr Ala Val Thr Thr Gly Asp His Gly Ile 550 555 Ile Arg Thr Leu Asp Leu Pro Ile Tyr Val Thr Arg Val Lys Gly Asn 565 570 575 Asn Val Tyr Cys Leu Asp Arg Glu Cys Arg Pro Arg Val Leu Thr Ile 580 585 Asp Pro Thr Glu Phe Lys Phe Lys Leu Ala Leu Ile Asn Arg Lys Tyr 595 600 605 Asp Glu Val Leu His Met Val Arg Asn Ala Lys Leu Val Gly Gln Ser 615 620 Ile Ile Ala Tyr Leu Gln Lys Lys Gly Tyr Pro Glu Val Ala Leu His 630 635 Phe Val Lys Asp Glu Lys Thr Arg Phe Ser Leu Ala Leu Glu Cys Gly 645 650 Asn Ile Glu Ile Ala Leu Glu Ala Ala Lys Ala Leu Asp Asp Lys Asn 660 665 Cys Trp Glu Lys Leu Gly Glu Val Ala Leu Leu Gln Gly Asn His Gln 680 685 Ile Val Glu Met Cys Tyr Gln Arg Thr Lys Asn Phe Asp Lys Val Ser 695 700 Phe Leu Tyr Leu Ile Thr Gly Asn Leu Glu Lys Leu Arg Lys Met Met 710 715 Lys Ile Ala Glu Ile Arg Lys Asp Met Ser Gly His Tyr Gln Asn Ala 725 730 Leu Tyr Leu Gly Asp Val Ser Glu Arg Val Arg Ile Leu Lys Asn Cys 740 745 Gly Gln Lys Ser Leu Ala Tyr Leu Thr Ala Ala Thr His Gly Leu Asp 760 Glu Glu Ala Glu Ser Leu Lys Glu Thr Phe Asp Pro Glu Lys Glu Thr 775 Ile Pro Asp Ile Asp Pro Asn Ala Lys Leu Gln Pro Pro Ala Pro 790 795 Ile Met Pro Leu Asp Thr Asn Trp Pro Leu Leu Thr Val Ser Lys Gly 805 810 Phe Phe Glu Gly Thr Ile Ala Ser Lys Gly Lys Gly Gly Ala Leu Ala 825 820 Ala Asp Ile Asp Ile Asp Thr Val Gly Thr Glu Gly Trp Gly Glu Asp 840 Ala Glu Leu Gln Leu Asp Glu Asp Gly Phe Val Glu Ala Thr Glu Gly

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91

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Pro Ser Leu Asn Gly Arg Arg Ile Ser Asp Pro Gln Val Phe Ser Lys
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Pro His Ser Tyr Thr Ser Thr Ala Val Ile Pro Asn Cys Gly Thr Pro
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Lys Gln Arg Ile Thr Ile Leu Gln Asn Ala Ser Ile Thr Pro Val Lys
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Ser Lys Thr Ser Thr Glu Asp Leu Met Asn Leu Glu Gln Gly Met Ser
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Ile Ile Cys Pro His Tyr Glu Asp His Ser Val Ala Asp Ala Ala Met
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Glu Gln Tyr Ile Leu Tyr Leu Val Glu His Glu Glu Tyr Gln Leu Cys
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Pro Phe Thr Leu Gly Lys Glu Phe Lys Glu Gly His Ser Tyr Tyr
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Ile Ser Lys Pro Ile His Gln His Glu Asp Arg Cys Leu Arg Leu Lys
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Val Thr Val Ser Gly Lys Ile Thr His Ser Pro Gln Ala His Val Asn
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Pro Gln Glu Lys Arg Leu Ala Ala Asp Asp Pro Glu Val Arg Val Leu
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<212> PRT

<213> Homo sapiens

<400> 52

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Thr	Phe 210	Arg	Ser	Met	Gly	Gly 215	Ala	Val	Ser	Ala	Ala 220	Glu	Leu	Leu	Glu
Val 225	Gly	Ile	Leu	Asp	Glu 230	Gln	Ala	Val	Gln	Gly 235	Leu	Arg	Glu	Gly	Arg 240
Leu	Ala	Ala	Val	Asp 245	Val	Ser	Ala	Arg	Ala 250	Glu	Val	Arg	Arg	Tyr 255	Leu
Glu	Gly	Thr	Gly 260	Ser	Val	Ala	Gly	Val 265	Val	Leu	Leu	Pro	Glu 270	Gly	His
Lys	Lys	Ser 275	Phe	Phe	Gln	Ala	Ala 280	Thr	Glu	His	Leu	Leu 285	Pro	Met	Gly
Thr	Ala 290	Leu	Pro	Leu	Leu	Glu 295	Ala	Gln	Ala	Ala	Thr 300	His	Thr	Leu	Val
305	Pro				310	-				315				-	320
Gly	Leu	Val	Ser	Pro 325	Glu	Leu	His	Glu	Gln 330	Leu	Leu	Val	Ala	Glu 335	Gln
Ala	Val	Thr	Gly 340	His	His	Asp	Pro	Phe 345	Ser	Gly	Ser	Gln	Ile 350	Pro	Leu
	Gln	355					360			_		365			_
	Leu 370		**			375					380				
385	Leu				390					395	_		-		400
	Asp			405					410					415	_
	His		420		_	_		425					430		
	Pro	435					440					445			
	Gly 450					455					460			_	
465	Leu				470					475	_	_		_	480
	Pro			485	_				490					495	
	Gln		500					505					510		
	Glu Thr	515					520					525			
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545					550					555	_				560
	Glu			565					570					575	
	Gln Gly		580					585					590		
	Leu	595					600					605	_		
	610 Gly					615					620				
625	Ala				630					635					640
	Ser			645					650					655	
	Gln		660					665					670		
GTII	11.11	116	DET	пеп	FILE	G7.11	лта	7.7C C	GTII	пЛэ	GTA	лец	TTE	val	ALG

680 Glu His Gly Ile Arg Leu Leu Glu Ala Gln Ile Ala Thr Gly Gly Val 695 700 Ile Asp Pro Val His Ser His Arg Val Pro Val Asp Val Ala Tyr Arg 710 715 Arg Gly Tyr Phe Asp Gln Met Leu Asn Leu Ile Leu Leu Asp Pro Ser 725 730 Asp Asp Thr Lys Gly Phe Phe Asp Pro Asn Thr His Glu Asn Leu Thr 745 Tyr Leu Gln Leu Leu Glu Arg Cys Val Arg Asp Pro Glu Thr Gly Leu 760 Tyr Leu Leu Pro Leu Ser Ser Thr Gln Ser Pro Leu Val Asp Ser Ala 775 Thr Gln Gln Ala Phe Gln Asn Leu Leu Leu Ser Val Lys Tyr Gly Arg 790 795 Phe Gln Gly Gln Arg Val Ser Ala Trp Glu Leu Ile Asn Ser Glu Tyr 805 810 Phe Ser Glu Gly Arg Arg Gln Leu Leu Arg Arg Tyr Arg Gln Arg 825 830 Glu Val Thr Leu Gly Gln Val Ala Lys Leu Leu Glu Ala Glu Thr Gln 840 Arg Gln Ala Asp Ile Met Leu Pro Ala Leu Arg Ser Arg Val Thr Val 850 855 860 His Gln Leu Leu Glu Ala Gly Ile Ile Asp Gln Gln Leu Leu Asp Gln 865 870 875 Val Leu Ala Gly Thr Ile Ser Pro Glu Ala Leu Leu Leu Met Asp Gly 885 890 Val Arg Arg Tyr Leu Cys Gly Leu Gly Ala Val Gly Gly Val Arg Leu 900 905 Leu Pro Ser Gly Gln Arg Leu Ser Leu Tyr Gln Ala Met Arg Gln Lys 920 Leu Leu Gly Pro Arg Val Ala Leu Ala Leu Leu Glu Ala Gln Ala Ala 930 935 940 Thr Gly Thr Ile Met Asp Pro His Ser Pro Glu Ser Leu Ser Val Asp 945 950 955 Glu Ala Val Arg Arg Gly Val Val Gly Pro Glu Leu Tyr Gly Arg Leu 965 970 975 Lys Arg Ala Glu Gly Ala Ile Ala Gly Phe Arg Asp Pro Phe Ser Gly 980 985 990 Lys Gln Val Ser Val Phe Gln Ala Met Lys Lys Gly Leu Ile Pro Trp 995 1000 1005 Glu Gln Ala Ala Arg Leu Leu Glu Ala Gln Val Ala Thr Gly Gly Ile 1010 1015 1020 Ile Asp Pro Thr Ser His His Leu Pro Met Pro Val Ala Ile Gln 1025 1030 1035 Arg Gly Tyr Val Asp Gln Glu Met Glu Thr Ala Leu Ser Ser Ser 1045 1050 1055 Glu Thr Phe Pro Thr Pro Asp Gly Gln Gly Arg Thr Ser Tyr Ala Gln 1060 1065 1070 Leu Leu Glu Glu Cys Pro Arg Asp Glu Thr Ser Gly Leu His Leu Leu 1075 1080 1085 Pro Leu Pro Glu Ser Ala Pro Ala Leu Pro Thr Glu Glu Gln Val Gln 1090 1095 1100 Arg Ser Leu Gln Ala Val Pro Gly Ala Lys Asp Gly Thr Ser Leu Trp 1105 1110 1115 Asp Leu Leu Ser Ser Cys His Phe Thr Glu Glu Gln Arg Arg Gly Leu 1125 1130 1135 Leu Glu Asp Val Gln Glu Gly Arg Thr Thr Val Pro Gln Leu Leu Ala 1145

 Ser Val
 Gln
 Arg
 Trp
 Val
 Gln
 Glu
 Thr
 Lys
 Leu
 Leu
 Ala
 Gln
 Ala
 Arg

 Val
 Met
 Val
 Pro
 Gly
 Gly
 Glu
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 Ala
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 Trp
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 Leu

 Asp
 Ala
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 Ile
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 Gln
 Glu
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 Leu
 Ala
 Leu
 Ala
 Gln
 Gly

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 1190
 1195
 1200

Thr Gln Ser Pro Ala Gln Val Ala Glu Gln Pro Ala Val Lys Ala Cys
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Val Asp Pro Leu Asn Asn Gln Arg Leu Ser Val Glu Asp Ala Val Lys 1265 1270 1275 1280

Val Gly Leu Val Gly Arg Glu Leu Ser Glu Gln Leu Gly Gln Ala Glu 1285 1290 1295

Arg Ala Ala Gly Tyr Pro Asp Pro Tyr Ser Arg Ala Ser Leu Ser 1300 1305 1310

Leu Trp Gln Ala Met Glu Lys Gly Leu Val Pro Gln Asn Glu Gly Leu 1315 1320 1325

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His Gly Val His Leu Pro Gln Ala Ala Cys Arg Leu Gly Leu Leu 1345 1350 1355 1360

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Phe Phe Phe Asp Pro Ser Ala Arg Asp Gln Val Thr Tyr Gln Gln Leu 1380 1385 1390

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Glu Leu Ser Gln Gly Thr Thr Thr Val Lys Glu Val Ala Glu Met Asp 1525 1530 1535

Ser Val Lys Arg Ser Leu Glu Gly Gly Asn Phe Ile Ala Gly Val Leu 1540 1545 1550

Ile Gln Gly Thr Gln Glu Arg Met Ser Ile Pro Glu Ala Leu Arg Arg 1555 1560 1565

His Ile Leu Arg Pro Gly Thr Ala Leu Val Leu Leu Glu Ala Gln Ala 1570 1580

Ala Thr Gly Phe Ile Ile Asp Pro Ala Glu Asn Arg Lys Leu Thr Val 1585 1590 1595 1600

Glu Glu Ala Phe Lys Ala Gly Met Phe Gly Lys Glu Thr Tyr Val Lys 1605 1610 1615

Leu Leu Ser Ala Glu Arg Ala Val Thr Gly Tyr Thr Asp Pro Tyr Thr

1620 1625 Gly Gln Gln Ile Ser Leu Phe Gln Ala Met Gln Lys Asp Leu Ile Val 1635 1640 1645 Arg Glu His Gly Ile Arg Leu Leu Glu Ala Gln Ile Ala Thr Gly Gly 1650 1655 1660 Ile Ile Asp Pro Val His Ser His Arg Val Pro Val Asp Val Ala Tyr 1665 1670 1675 1680 Arg Cys Gly Tyr Phe Asp Glu Glu Met Asn Arg Ile Leu Ala Asp Pro 1685 1690 1695 Ser Asp Asp Thr Lys Gly Phe Phe Asp Pro Asn Thr His Glu Asn Leu 1700 1705 1710 Thr Tyr Leu Gln Leu Leu Glu Arg Cys Val Glu Asp Pro Glu Thr Gly 1715 1720 1725 Leu Tyr Leu Leu Gln Ile Ile Lys Lys Gly Glu Asn Tyr Val Tyr Ile 1730 1735 1740
Asn Glu Ala Thr Arg His Val Leu Gln Ser Arg Thr Ala Lys Met Arg 1745 1750 1755 1760 Val Gly Arg Phe Ala Asp Gln Val Val Ser Phe Trp Asp Leu Leu Ser 1765 1770 1775 Ser Pro Tyr Phe Thr Glu Asp Arg Lys Arg Glu Leu Ile Gln Glu Tyr 1780 1785 1790 Gly Ala Gln Ser Gly Gly Leu Glu Lys Leu Leu Glu Ile Ile Thr Thr 1795 1800 1805 Thr Ile Glu Glu Thr Glu Thr Gln Asn Gln Gly Ile Lys Val Ala Ala $1810 \hspace{1.5cm} 1815 \hspace{1.5cm} 1820 \\ \hbox{Ile Arg Gly Glu Val Thr Ala Ala Asp Leu Phe Asn Ser Arg Val Ile} \\$ 1825 1830 1835 1840 Asp Gln Lys Thr Leu His Thr Leu Arg Val Gly Arg Thr Gly Gly Gln 1845 1850 1855 Ala Leu Ser Thr Leu Glu Cys Val Lys Pro Tyr Leu Glu Gly Ser Asp 1860 1865 1870 Cys Ile Ala Gly Val Thr Val Pro Ser Thr Arg Glu Val Met Ser Leu 1875 1880 1885 His Glu Ala Ser Arg Lys Glu Leu Ile Pro Ala Ala Phe Ala Thr Trp 1890 1895 1900 Leu Leu Glu Ala Gln Ala Ala Thr Gly Phe Leu Leu Asp Pro Cys Thr 1905 1910 1915 1920 Arg Gln Lys Leu Ser Val Asp Glu Ala Val Asp Val Gly Leu Val Asn 1925 1930 1935 Glu Glu Leu Arg Glu Arg Leu Leu Lys Ala Glu Arg Ala Ala Thr Gly 1940 1945 1950 Tyr Arg Asp Pro Ala Thr Gly Asp Thr Ile Pro Leu Phe Gln Ala Met 1955 1960 1965 Gln Lys Gln Leu Ile Glu Lys Ala Glu Ala Leu Arg Leu Leu Glu Val 1970 1975 1980 Gln Val Ala Thr Gly Gly Val Ile Asp Pro Gln His His Arg Leu 1985 1990 1995 2000 Pro Leu Glu Thr Ala Tyr Arg Arg Gly Cys Leu His Lys Asp Ile Tyr 2005 2010 2015 Ala Leu Ile Ser Asp Gln Lys His Met Arg Lys Arg Phe Val Asp Pro 2020 2025 2030 Asn Thr Gln Glu Lys Val Ser Tyr Arg Glu Leu Gln Glu Arg Cys Arg 2035 2040 Pro Gln Glu Asp Thr Gly Trp Val Leu Phe Pro Val Asn Lys Ala Ala 2050 2055 Arq Asp Ser Glu His Ile Asp Asp Glu Thr Arg Arg Ala Leu Glu Ala 2065 2070 2075 2080 Glu Gln Val Glu Ile Thr Val Gly Arg Phe Arg Gly Gln Lys Pro Thr 2090

Leu Trp Ala Leu Leu Asn Ser Glu Tyr Val Thr Glu Glu Lys Lys Leu 2100 2105 2110 Gln Leu Val Arg Met Tyr Arg Thr His Thr Arg Arg Ala Leu Gln Thr 2115 2120 Val Ala Gln Leu Ile Leu Glu Leu Ile Glu Lys Gln Glu Thr Ser Asn 2130 2135 2140 Lys His Leu Trp Phe Gln Gly Ile Arg Arg Gln Ile Thr Ala Ser Glu 2145 2150 2155 2160 Leu Leu Ser Ser Ala Ile Ile Thr Glu Glu Met Leu Gln Asp Leu Glu 2165 2170 2175 Thr Gly Arg Ser Thr Thr Gln Glu Leu Met Glu Asp Asp Arg Val Lys 2180 2185 2190 Arg Tyr Leu Glu Gly Thr Ser Cys Ile Ala Gly Val Leu Val Pro Ala 2195 2200 2205 Lys Asp Gln Pro Gly Arg Gln Glu Lys Met Ser Ile Tyr Gln Ala Met 2210 2215 2220 Trp Lys Gly Val Leu Arg Pro Gly Thr Ala Leu Val Leu Leu Glu Ala 2230 2235 2240 Gln Ala Ala Thr Gly Phe Val Ile Asp Pro Val Arg Asn Leu Arg Leu 2245 2250 2255 Ser Val Glu Glu Pro Val Pro Ala Gly Val Val Gly Ser Glu Ile Gln 2260 2265 2270 Glu Lys Leu Leu Ser Ala Glu Arg Ala Val Thr Gly Tyr Thr Asp Pro 2275 2280 2285 Tyr Thr Gly Gln Gln Ile Ser Leu Phe Gln Ala Met Gln Lys Asp Leu 2290 2295 2300 Ile Val Arg Glu His Gly Ile Arg Leu Leu Glu Ala Gln Ile Ala Thr 2310 2315 2320 Gly Val Ile Asp Pro Val His Ser His Arg Val Pro Val Asp Val 2325 2330 2335 Ala Tyr Arg Arg Gly Tyr Phe Asp Glu Glu Met Asn Arg Val Leu Ala 2340 2345 2350 Asp Pro Ser Asp Asp Thr Lys Gly Phe Phe Asp Pro Asn Thr His Glu 2355 2360 2365 Asn Leu Thr Tyr Val Gln Leu Leu Arg Arg Cys Val Pro Asp Pro Asp 2370 2375 2380 Thr Gly Leu Tyr Met Leu Gln Leu Ala Gly Arg Gly Ser Ala Val His 2390 2395 2400 Gln Leu Ser Glu Glu Leu Arg Cys Ala Leu Arg Asp Ala Arg Val Thr 2405 2410 2415 Pro Gly Ser Gly Ala Leu Gln Gly Gln Ser Val Ser Val Trp Glu Leu 2420 2425 2430 Leu Phe Tyr Arg Glu Val Ser Glu Asp Arg Arg Gln Asp Leu Leu Ser 2435 2440 2445 Arg Tyr Arg Ala Gly Thr Leu Thr Val Glu Glu Leu Gly Ala Thr Leu 2455 2460 Thr Ser Leu Leu Ala Gln Ala Gln Ala Gln Ala Arg Ala Glu Ala Glu 2470 2475 Ala Gly Ser Pro Arg Pro Asp Pro Arg Glu Ala Leu Arg Ala Ala Thr 2485 2490 Met Glu Val Lys Val Gly Arg Leu Arg Gly Arg Ala Val Pro Val Trp 2500 2505 Asp Val Leu Ala Ser Gly Tyr Val Ser Arg Ala Ala Arg Glu Glu Leu 2520 2525 Leu Ala Glu Phe Gly Ser Gly Thr Leu Asp Leu Pro Ala Leu Thr Arg 2535 2540 Arg Leu Thr Ala Ile Ile Glu Glu Ala Glu Glu Ala Pro Gly Ala Arg 2550 2555 Pro Gln Leu Gln Asp Ala Arg Arg Gly Pro Arg Glu Pro Gly Pro Ala

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Gln	Glu 2610		Thr	Leu	Arg	Asp 261		Thr	Met	Glu	Val 2620		Arg	Gly	Gln
Phe 2625	Gln 5	Gly	Arg	Pro	Val 2630		Val	Trp	Asp	Val 263		Phe	Ser	Ser	Tyr 2640
Leu	Ser	Glu	Ala	Arg 264		Asp	Glu	Leu	Leu 2650		Gln	His	Ala	Ala 265	Gly 5
Ala	Leu	Gly	Leu 2660		Asp	Leu	Val	Ala 266		Leu	Thr	Arg	Val 267		Glu
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Gln	Val 2690		Ala	Ser	Glu	Leu 2695		Thr	Ser	Gly	Ile 2700		Gly	Pro	Glu
Thr 2705	Leu	Arg	Asp	Leu	Ala 271		Gly	Thr	Lys	Thr 271		Gln	Glu	Val	Thr 2720
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	Val		2740)				2745	5				2750)	
	Ile	2755	5				2760)				276	ō		
	Val 2770)				2775	5				2780)		-	
2785					2790)				2795	5			-	2800
	Gly			2805	ō				2810)			_	281	5
	Gly		2820)				2825	5				2830)	
	Met	2835	5				2840)				2845	5		
	Ala 2850)				2855	5				2860)			
2865					2870)				2875	5		_		2880
	Asn			2885	5				2890)				2895	5
	Pro		2900)				2905	5				2910)	
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	Gly 2930)				2935	5				2940)			
2945					2950)				2955	5				2960
	Ser			2965	5				2970)				2975	5
	Gln		2980)				2985	5				2990)	
	Leu	2995	5				3000)				3005	5		
	Arg 3010)				3015	5				3020)			
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Leu Pro Ala Leu Thr Ar 3075	g Arg Leu 3080		e Ile Glu 308		Glu
Glu Ala Pro Gly Ala Ar 3090	g Pro Gln 3095	Leu Gln As	p Ala Trp 3100	Arg Gly	Pro
Arg Glu Pro Gly Pro Al 3105 31	a Gly Arg 10	Gly Asp Gl		Gly Arg	Ser 3120
Gln Arg Glu Gly Gln Gl 3125	y Glu Gly	Glu Thr Gl: 3130	n Glu Ala	Ala Ala 313	
Ala Ala Ala Arg Ar 3140		3145	_	3150	
Glu Val Gln Arg Gly Gl 3155	n Phe Gln 3160		o Val Ser 316		Asp
Val Leu Phe Ser Ser Ty 3170	3175		3180		
	90	31	95		3200
Leu Thr Arg Val Ile Gl 3205		3210		3215	5
Phe Arg Gly Leu Arg Ar 3220		3225		3230	
Gly Ile Leu Gly Pro Gl 3235	3240) -	324	5	-
Thr Leu Gln Glu Val Th 3250	3255		3260		
	70	32	75		3280
Gly Arg Gln Glu Lys Me 3285		3290		3295	5
Leu Arg Pro Gly Thr Al		3305		3310	
Gly Phe Val Ile Asp Pr 3315	3320		g Leu Ser 332		Glu
Ala Val Ala Ala Gly Va 3330	3335		3340	Lys Leu	
Ala Val Ala Ala Gly Va 3330 Ser Ala Glu Arg Ala Va 3345 33	3335 1 Thr Gly 50	Tyr Thr Ass	3340 p Pro Tyr 55	Lys Leu Thr Gly	Gln 3360
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Ala Val Ala Ala Gly Va 3330 Ser Ala Glu Arg Ala Va 3345 33 Gln Ile Ser Leu Phe Gl 3365 His Gly Ile Arg Leu Le 3380 Asp Pro Val His Ser Hi 3395	3335 1 Thr Gly 50 n Ala Met u Glu Ala s Arg Val 3400	Tyr Thr Asy 33 Gln Lys Asy 3370 Gln Ile Ald 3385 Pro Val Asy	3340 p Pro Tyr 55 p Leu Ile a Thr Gly p Val Ala 340	Lys Leu Thr Gly Val Arg 3375 Gly Val 3390 Tyr Arg 5	Gln 3360 Glu 5 Ile Arg
Ala Val Ala Ala Gly Va 3330 Ser Ala Glu Arg Ala Va 3345 Gln Ile Ser Leu Phe Gl 3365 His Gly Ile Arg Leu Le 3380 Asp Pro Val His Ser Hi 3395 Gly Tyr Phe Asp Glu Gl 3410	3335 1 Thr Gly 50 n Ala Met u Glu Ala s Arg Val 3400 u Met Asn 3415	Tyr Thr Asy 33 Gln Lys Asy 3370 Gln Ile Al 3385 Pro Val Asy Arg Val Le	3340 p Pro Tyr 55 p Leu Ile a Thr Gly p Val Ala 340 u Ala Asp 3420	Lys Leu Thr Gly Val Arg 3375 Gly Val 3390 Tyr Arg 5 Pro Ser	Gln 3360 Glu 5 Ile Arg
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Ala Val Ala Ala Gly Van 3330 Ser Ala Glu Arg Ala Van 3345 Gln Ile Ser Leu Phe Gl 3365 His Gly Ile Arg Leu Leu 3380 Asp Pro Val His Ser Hi 3395 Gly Tyr Phe Asp Glu Gl 3410 Asp Thr Lys Gly Phe Ph 3425 Val Gln Leu Leu Arg Arg Arg Met Leu Gln Leu Ala Gl 3460	3335 1 Thr Gly 50 n Ala Met u Glu Ala s Arg Val 3400 u Met Asn 3415 e Asp Pro 30 g Cys Val y Arg Gly	Tyr Thr As; 33 Gln Lys As; 3370 Gln Ile Al. 3385 Pro Val As; Arg Val Le: Asn Thr Hi. 34 Pro Asp Pro 3450 Ser Ala Va.	3340 p Pro Tyr 55 p Leu Ile a Thr Gly p Val Ala 340 u Ala Asp 3420 s Glu Asn 35 o Asp Thr	Lys Leu Thr Gly Val Arg 3375 Gly Val 3390 Tyr Arg 5 Pro Ser Leu Thr Gly Leu 3455 Leu Ser 3470	Gln 3360 Glu 5 Ile Arg Asp Tyr 3440 Tyr 5
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Ala Val Ala Ala Gly Va 3330 Ser Ala Glu Arg Ala Va 3345 Gln Ile Ser Leu Phe Gl 3365 His Gly Ile Arg Leu Le 3380 Asp Pro Val His Ser Hi 3395 Gly Tyr Phe Asp Glu Gl 3410 Asp Thr Lys Gly Phe Ph 3425 Val Gln Leu Leu Arg	3335 1 Thr Gly 50 n Ala Met u Glu Ala s Arg Val 3400 u Met Asn 3415 e Asp Pro 30 g Cys Val y Arg Gly u Arg Asp 3480 r Val Ser 3495	Tyr Thr As; 33 Gln Lys As; 3370 Gln Ile Al. 3385 Pro Val As; Arg Val Le: Asn Thr Hi. 34 Pro Asp Pro 3450 Ser Ala Va. 3465 Ala Arg Val Val Trp Gl:	3340 p Pro Tyr 55 p Leu Ile a Thr Gly p Val Ala 340 u Ala Asp 3420 s Glu Asn 35 o Asp Thr l His Gln l Thr Pro 348 u Leu Leu 3500	Lys Leu Thr Gly Val Arg 3375 Gly Val 3390 Tyr Arg 5 Pro Ser Leu Thr Gly Leu 3455 Leu Ser 3470 Gly Ser 5 Phe Tyr	Gln 3360 Glu 5 Ile Arg Asp Tyr 3440 Tyr 6 Glu Gly Arg

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Pro Asp Thr Gly Leu Tyr Met Leu Gln Leu Ala Gly Arg Gly Ser Ala 3985 3990 3995 4000 Val His Gln Leu Ser Glu Glu Leu Arg Cys Ala Leu Arg Asp Ala Arg 4005 4010 4015 Val Thr Pro Gly Ser Gly Ala Leu Gln Gly Gln Ser Val Ser Val Trp 4020 4025 Glu Leu Leu Phe Tyr Arg Glu Val Ser Glu Asp Arg Arg Gln Asp Leu 4035 4040 4045 Leu Ser Arg Tyr Arg Ala Ser Thr Leu Thr Val Glu Glu Leu Gly Ala 4050 4055 4060 Thr Leu Thr Ser Leu Leu Ala Gln Ala Gln Ala Gln Ala Arg Ala Glu 4070 4075 4080 Ala Glu Ala Gly Ser Pro Arg Pro Asp Pro Arg Glu Ala Leu Arg Ala 4085 4090 4095 Ala Thr Met Glu Val Lys Val Gly Arg Leu Arg Gly Arg Ala Val Pro 4100 4105 4110 Val Trp Asp Val Leu Ala Ser Gly Tyr Val Ser Arg Ala Ala Arg Glu 4115 4120 4125 Glu Leu Leu Ala Glu Phe Gly Ser Gly Thr Leu Asp Leu Pro Ala Leu 4130 4135 4140 Thr Arg Arg Leu Thr Ala Ile Ile Glu Glu Ala Glu Glu Ala Pro Gly 4150 4155 4160 Ala Arg Pro; Gln Leu Gln Asp Ala Trp Arg Gly Pro Arg Glu Pro Gly 4165 4170 4175 Pro Ala Gly Arg Gly Asp Gly Asp Ser Gly Arg Ser Gln Arg Glu Gly 4180 4185 4190 Gln Gly Glu Gly Glu Thr Gln Glu Ala Ala Ala Ala Thr Ala Ala Ala 4195 4200 4205 Arg Arg Gln Glu Gln Thr Leu Arg Asp Ala Thr Met Glu Val Gln Arg 4210 4215 4220 Gly Gln Phe Gln Gly Arg Pro Val Ser Val Trp Asp Val Leu Phe Ser 4230 4235 4240 Ser Tyr Leu Ser Glu Ala Arg Arg Asp Glu Leu Leu Ala Gln His Ala 4245 4250 4255 Ala Gly Ala Leu Gly Leu Pro Asp Leu Val Ala Val Leu Thr Arg Val 4260 4265 4270 Ile Glu Glu Thr Glu Glu Arg Leu Ser Lys Val Ser Phe Arg Gly Leu 4275 4280 4285 Arg Arg Gln Val Ser Ala Ser Glu Leu His Thr Ser Gly Ile Leu Gly 4290 4295 4300 Pro Glu Thr Leu Arg Asp Leu Ala Gln Gly Thr Lys Thr Leu Gln Glu 4310 4315 Val Thr Glu Met Asp Ser Val Lys Arg Tyr Leu Glu Gly Thr Ser Cys 4325 4330 Ile Ala Gly Val Leu Val Pro Ala Lys Asp Gln Pro Gly Arg Gln Glu 4340 4345 4350 Lys Met Ser Ile Tyr Gln Ala Met Trp Lys Gly Val Leu Arg Pro Gly 4360 Thr Ala Leu Val Leu Leu Glu Ala Gln Ala Ala Thr Gly Phe Val Ile 4375 4380 Asp Pro Val Arg Asn Leu Arg Leu Ser Val Glu Glu Ala Val Ala Ala 4390 4395 Gly Val Val Gly Glu Ile Gln Glu Lys Leu Leu Ser Ala Glu Arg 4410 4405 Ala Val Thr Gly Tyr Thr Asp Pro Tyr Thr Gly Gln Gln Ile Ser Leu 4420 4425 Phe Gln Ala Met Gln Lys Asp Leu Ile Val Arg Glu His Gly Ile Arg 4440 Leu Leu Glu Ala Gln Ile Ala Thr Gly Gly Val Ile Asp Pro Val His

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Phe	Phe	Asp	Pro 4500		Thr	His	Glu	Asn 4505		Thr	Tyr	Val	Gln 451	Leu)	Leu
Arg	Arg	Cys 4515		Pro	Asp	Pro	Asp 4520		Gly	Leu	Tyr	Met 4525		Gln	Leu
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Ala 4545		Arg	Asp	Ala	Arg 4550		Thr	Pro	Gly	Ser 4555		Ala	Leu	Gln	Gly 4560
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Val	Glu	Glu 4595		Gly	Ala	Thr	Leu 4600		Ser	Leu	Leu	Ala 4605	_	Ala	Gln
Ala	Gln 461		Arg	Ala	Glu	Ala 4615		Ala	Gly	Ser	Pro 4620		Pro	Asp	Pro
4625	5			_	4630)				4635	5		_	Arg	4640
				4645	õ				4650)				Tyr 4655	, ,
Ser	Gly	Ala	Ala 4660		Glu	Glu	Leu	Leu 4665		Glu	Phe	Gly	Ser 4670	Gly)	Thr
Leu	Asp	Leu 4675		Ala	Leu	Thr	Arg 4680	_	Leu	Thr	Ala	Ile 4685		Glu	Glu
	Glu 4690		Ala	Pro	Gly	Ala 4695	-	Pro	Gln	Leu	Gln 4700	_	Ala	Trp	Arg
4705	5				4710)				4715	5	_	_	Ser	4720
				4725	5		-		4730)				Ala 4735	
			4740)				4745	5				4750		
		4755	5				4760)				4765	5	Ser	
	4770)				4775	5				4780)		Asp	
4785	5				4790)				4795	ō			Leu	4800
				4805	5				4810)		_		Ser 4815	_
			4820)				4825	;				4830		
		4835	5				4840)				4845	5	Gln	
	4850)				4855	5				4860)		Arg	_
4865	5				4870)				4875	5				4880
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			4900)				4905	,				4910		
Ala	Thr	Gly 4915		Val	Ile	Asp	Pro 4920		Arg	Asn	Leu	Arg 4925		Ser	Val

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<212> PRT

<213> Homo sapiens

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110

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<211> 509

<212> PRT

<213> Homo sapiens

<400> 56

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	50		Glu			55					60			_	_
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Ser	Tyr 210	Ser	Val	Asp	Ala	Ala 215	Glu	Val	Thr	Glu	Leu 220	His	Val	Ile	Ser
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Gly	Glu	Ile	Ser	Ser 405	Arg	Tyr	Lys	Ala	Asp 410		Ser	Pro	Glu	Asn 415	
Lys	Leu	Leu	Ser 420	Thr	Phe	Leu	Asn	Gln 425	Thr	Gly	Leu	Asp	Ala 430	Phe	Leu
Leu	Glu	Leu 435	His	Glu	Met	Ile	Ile 440	Leu	Lys	Leu	Lys	Asn 445	Pro	Gln	Thr
Gln	Thr 450	Glu	Glu	Arg	Phe	Arg 455	Pro	Gln	Trp	Ser	Leu 460	Arg	Asp	Thr	Leu
Val 465	Ser	Tyr	Met	Gln	Thr 470	Lys	Glu	Ser	Glu	Ile 475	Leu	Pro	Glu	Met	Ala 480
	Gln	Phe	Pro	Glu 485		Ile	Leu	Leu	Ala 490		Cys	Val	Ser	Val 495	
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112

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Leu Glu Ser Ser Asp Cys Glu Ser Leu Asp Ser Ser Asn Ser Gly Phe
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Gly Pro Glu Glu Asp Thr Ala Tyr Leu Asp Gly Val Ser Leu Pro Asp
                    70
                                        75
Phe Glu Leu Leu Ser Asp Pro Glu Asp Glu His Leu Cys Ala Asn Leu
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Met Gln Leu Leu Gln Glu Ser Leu Ala Gln Ala Arg Leu Gly Ser Arg
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<210> 59 <211> 2012 <212> DNA <213> Homo sapiens

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115

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Thr Gly Asp Met Gly Ser Leu Asp Asp Pro Lys Met Lys Ser Met Met 450

Pro Thr Asp Glu Gln Phe Ala Ala Ile Ile Val Leu Gly Phe Ala Thr 465

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Cys Asp Asn Cys Arg Arg Pro Gly Gly Glu Pro Ser Pro Glu Gly Thr
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Thr Tyr Tyr 945	Phe Lys	Val Phe 950	Ala Val	Ser Hi. 95.		Arg G	lu Ser	Lys 960
Pro Leu Thr	Ala Gln 965	Gln Thr	Thr Lys	Leu As 970	o Ala	Pro T	nr Asn 975	Leu
Gln Phe Val	Asn Glu 980	Thr Asp	Ser Thi		ı Val		rp Thr 90	Pro
Pro Arg Ala 995		Thr Gly	Tyr Arg	J Leu Th	r Val	Gly Le 1005	eu Thr	Arg
Arg Gly Gln 1010	Pro Arg	Gln Tyr 101		. Gly Pro	Ser 1020		er Lys	Tyr
Pro Leu Arg 1025		1030		10	35			1040
Ala Ile Lys	Gly Asn 104		Ser Pro	Lys Al: 1050	a Thr	Gly Va	al Phe 105	
Thr Leu Gln	1060		106	55		1	070	
Glu Thr Thr 107	5		1080			1085		
Lys Leu Gly 1090		109	5		1100)		
Thr Ser Asp 1105		1110		11:	15			1120
Glu Tyr Val	1125	5		1130			113	5
Ala Pro Ile	1140		114	. 5		1:	150	
Leu His Leu 115	5		1160			1165		
Glu Arg Ser 1170		117	5		1180)		
Pro Thr Asn 1185		1190		119	95			1200
Asp Gln Ser	1205	ō		1210			1215	5
Asn Val Ser	1220		122	:5		12	230	
Ser Asp Thr 123	5		1240			1245		
Thr Asn Ile 1250		125	5		1260)		
Ser Ile Asp 1265	Leu Thr	Asn Phe 1270	Leu Val	Arg Ty:		Pro Va	al Lys	Asn 1280
Glu Glu Asp	Val Ala 1285	Glu Leu	Ser Ile			Asp As	n Ala 1299	Val
Val Leu Thr			Gly Thr	Glu Ty	val			

Ser Val	Tyr 131		Gln	His	Glu	Ser 132		Pro	Leu	Arg	Gly 1329		Gln	Lys
Thr Gly 1330		Asp	Ser	Pro	Thr 133		Ile	Asp	Phe	Ser 134		Ile	Thr	Ala
Asn Ser 1345	Phe	Thr	Val	His 1350	-	Ile	Ala	Pro	Arg 135		Thr	Ile	Thr	Gly 1360
Tyr Arg	Ile	Arg	His 1365		Pro	Glu	His	Phe 1370		Gly	Arg	Pro	Arg 137	
Asp Arg	Val	Pro 1380		Ser	Arg	Asn	Ser 1385		Thr	Leu	Thr	Asn 1390		Thr
Pro Gly	Thr 139		Tyr	Val	Val	Ser 140		Val	Ala	Leu	Asn 1405	_	Arg	Glu
Glu Ser 1410		Leu	Leu	Ile	Gly 1415		Gln	Ser	Thr	Val 1420		Asp	Val	Pro
Arg Asp 1425	Leu	Glu	Val	Val 1430		Ala	Thr	Pro	Thr 1435		Leu	Leu	Ile	Ser 1440
Trp Asp	Ala	Pro	Ala 1445		Thr	Val	Arg	Tyr 1450		Arg	Ile	Thr	Tyr 1455	_
Glu Thr		1460	C				1465	5				1470) _	
Lys Ser	147	5				1480)				1485	5	-	
Ile Thr 1490		Tyr	Ala	Val	Thr 1495		Arg	Gly	Asp	Ser 1500		Ala	Ser	Ser
Lys Pro 1505				1510)				1515	5	_			1520
Met Gln	Val	Thr	Asp 1525		Gln	Asp	Asn	Ser 1530		Ser	Val	Lys	Trp 1535	
Pro Ser	Ser		Pro	Val	Thr	Gly	Tyr	Arg	Val	Thr	Thr	Thr	Pro	Lys
		1540	-				1545					1550		
Asn Gly	155	Gly 5	Pro			1560	Lys)	Thr			1565	Asp	Gln	
Glu Met 1570	1559 Thr)	Gly 5 Ile	Pro Glu	Gly	Leu 1575	1560 Gln	Lys) Pro	Thr Thr	Val	Glu 1580	1565 Tyr)	Asp Val	Gln Val	Ser
Glu Met 1570 Val Tyr 1585	1559 Thr) Ala	Gly Tle Gln	Pro Glu Asn	Gly Pro 1590	Leu 1575 Ser)	1560 Gln Gly	Lys) Pro Glu	Thr Thr Ser	Val Gln 1595	Glu 1580 Pro	1565 Tyr) Leu	Asp Val Val	Gln Val Gln	Ser Thr 1600
Glu Met 1570 Val Tyr 1585 Ala Val	1559 Thr) Ala Thr	Gly Ile Gln Asn	Pro Glu Asn Ile 1605	Gly Pro 1590 Asp	Leu 1575 Ser) Arg	1560 Gln Gly Pro	Lys Pro Glu Lys	Thr Thr Ser Gly 1610	Val Gln 1595 Leu	Glu 1580 Pro Ala	1565 Tyr) Leu Phe	Asp Val Val Thr	Gln Val Gln Asp 1615	Ser Thr 1600 Val
Glu Met 1570 Val Tyr 1585 Ala Val Asp Val	1559 Thr) Ala Thr	Gly Ile Gln Asn Ser 1620	Pro Glu Asn Ile 1605 Ile	Gly Pro 1590 Asp Lys	Leu 1575 Ser) Arg Ile	1560 Gln Gly Pro	Lys Pro Glu Lys Trp 1625	Thr Thr Ser Gly 1610 Glu	Val Gln 1595 Leu) Ser	Glu 1580 Pro Ala Pro	1565 Tyr) Leu Phe Gln	Asp Val Val Thr Gly 1630	Gln Val Gln Asp 1615 Gln	Ser Thr 1600 Val Val
Glu Met 1570 Val Tyr 1585 Ala Val Asp Val Ser Arg	1555 Thr Ala Thr Asp Tyr 1635	Gly Ile Gln Asn Ser 1620 Arg	Pro Glu Asn Ile 1605 Ile Val	Gly Pro 1590 Asp Lys Thr	Leu 1575 Ser) Arg Ile	Gly Pro Ala Ser 1640	Lys Pro Glu Lys Trp 1625 Ser	Thr Ser Gly 1610 Glu Pro	Val Gln 1595 Leu) Ser	Glu 1580 Pro Ala Pro	1565 Tyr) Leu Phe Gln Gly 1645	Asp Val Val Thr Gly 1630 Ile	Gln Val Gln Asp 1615 Gln His	Ser Thr 1600 Val Val Glu
Glu Met 1570 Val Tyr 1585 Ala Val Asp Val Ser Arg Leu Phe 1650	1555 Thr Ala Thr Asp Tyr 1635 Pro	Gly Ile Gln Asn Ser 1620 Arg	Pro Glu Asn Ile 1605 Ile Val Pro	Pro 1590 Asp Lys Thr	Leu 1575 Ser) Arg Ile Tyr Gly 1655	1560 Gln Gly Pro Ala Ser 1640 Glu	Lys Pro Glu Lys Trp 1625 Ser Glu	Thr Thr Ser Gly 1610 Glu Fro Asp	Val Gln 1595 Leu Ser Glu	Glu 1580 Pro Ala Pro Asp Ala 1660	1565 Tyr) Leu Phe Gln Gly 1645 Glu	Asp Val Val Thr Gly 1630 Ile	Gln Val Gln Asp 1615 Gln His	Ser Thr 1600 Val Val Glu
Glu Met 1570 Val Tyr 1585 Ala Val Asp Val Ser Arg Leu Phe 1650 Leu Arg 1665	1555 Thr Ala Thr Asp Tyr 1635 Pro	Gly Ile Gln Asn Ser 1620 Arg Arg Ala	Pro Glu Asn Ile 1605 Ile Val Pro Ser	Pro 1590 Asp Lys Thr Asp Glu 1670	Leu 1575 Ser Arg Ile Tyr Gly 1655	1560 Gln Gly Pro Ala Ser 1640 Glu	Lys Pro Glu Lys Trp 1625 Ser Glu Val	Thr Ser Gly 1610 Glu Fro Asp	Val Gln 1595 Leu Ser Glu Thr Val 1675	Glu 1580 Pro Ala Pro Asp Ala 1660 Val	1565 Tyr) Leu Phe Gln Gly 1645 Glu) Ala	Asp Val Val Thr Gly 1630 Ile Leu	Gln Val Gln Asp 1615 Gln His Gln His	Thr 1600 Val Val Glu Gly Asp 1680
Glu Met 1570 Val Tyr 1585 Ala Val Asp Val Ser Arg Leu Phe 1650 Leu Arg 1665 Asp Met	1555 Thr Ala Thr Asp Tyr 1635 Pro Glu	Gly Ile Gln Asn Ser 1620 Arg Arg Ala Gly Ser	Pro Glu Asn Ile 1605 Ile Val Pro Ser Gln 1685	Pro 1590 Asp Lys Thr Asp Glu 1670 Pro	Leu 1575 Ser Arg Ile Tyr Gly 1655 Tyr	1560 Gln Gly Pro Ala Ser 1640 Glu Thr	Lys Pro Glu Lys Trp 1625 Ser Glu Val	Thr Thr Ser Gly 1610 Glu Fro Asp Ser Thr 1690	Val Gln 1595 Leu Ser Glu Thr Val 1675 Gln	Glu 1580 Pro Ala Pro Asp Ala 1660 Val	1565 Tyr Leu Phe Gln Gly 1645 Glu Ala	Asp Val Val Thr Gly 1630 Ile Leu Leu	Gln Val Gln Asp 1615 Gln His Gln His	Ser Thr 1600 Val Val Glu Gly Asp 1680 Pro
Glu Met 1570 Val Tyr 1585 Ala Val Asp Val Ser Arg Leu Phe 1650 Leu Arg 1665 Asp Met Ala Pro	1555 Thr Ala Thr Asp Tyr 1635 Pro Glu Thr	Gly Ile Gln Asn Ser 1620 Arg Arg Ala Gly Ser Asp	Pro Glu Asn Ile 1605 Ile Val Pro Ser Gln 1685 Leu	Pro 1590 Asp Lys Thr Asp Glu 1670 Pro	Leu 1575 Ser Arg Ile Tyr Gly 1655 Tyr Leu	1560 Gln Gly Pro Ala Ser 1640 Glu Thr Ile	Lys Pro Glu Lys Trp 1625 Ser Glu Val Gly Gln 1705	Thr Thr Ser Gly 1610 Glu Fro Asp Ser Thr 1690 Val	Val Gln 1595 Leu Ser Glu Thr Val 1675 Gln Thr	Glu 1580 Pro Ala Pro Asp Ala 1660 Val Ser	1565 Tyr Leu Phe Gln Gly 1645 Glu Ala Thr	Asp Val Val Thr Gly 1630 Ile Leu Leu Ala Ser 1710	Gln Val Gln Asp 1615 Gln His Gln His Leu	Ser Thr 1600 Val Val Glu Gly Asp 1680 Pro
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Glu Met 1570 Val Tyr 1585 Ala Val Asp Val Ser Arg Leu Phe 1650 Leu Arg 1665 Asp Met Ala Pro Ala Gln Val Thr 1730	1555 Thr Ala Thr Asp Tyr 1635 Pro Glu Thr Trp 1715 Pro	Gly Ile Gln Asn Ser 1620 Arg Ala Gly Ser Asp 1700 Thr Lys	Pro Glu Asn Ile 1605 Ile Val Pro Ser Gln 1685 Leu Pro Glu	Pro 1590 Asp Lys Thr Asp Glu 1670 Pro Lys Pro	Leu 1575 Ser Arg Ile Tyr Gly 1655 Tyr Leu Phe Asn	1560 Gln Gly Pro Ala Ser 1640 Glu Thr Ile Thr Val 1720 Gly	Lys Pro Glu Lys Trp 1625 Ser Glu Val Gly Gln 1705 Gln Pro	Thr Thr Ser Gly 1610 Glu Fro Asp Ser Thr 1690 Val Leu Met	Val Gln 1595 Leu Ser Glu Thr Val 1675 Gln Thr Thr	Glu 1580 Pro Ala Pro Asp Ala 1660 Val Ser Pro Gly Glu 1740	1565 Tyr Leu Phe Gln Gly 1645 Glu Ala Thr Tyr 1725 Ile	Val Val Thr Gly 1630 Leu Leu Ala Ser 1710 Arg	Gln Val Gln Asp 1615 Gln His Gln His Leu Val	Thr 1600 Val Val Glu Gly Asp 1680 Pro Ser Arg
Glu Met 1570 Val Tyr 1585 Ala Val Asp Val Ser Arg Leu Phe 1650 Leu Arg 1665 Asp Met Ala Pro Ala Gln Val Thr 1730 Pro Asp 1745	1555 Thr Ala Thr Asp Tyr 1635 Pro Glu Thr Trp 1715 Pro Ser	Gly Ile Gln Asn Ser 1620 Arg Ala Gly Ser Asp 1700 Thr Lys Ser	Pro Glu Asn Ile 1605 Ile Val Pro Ser Gln 1685 Leu Pro Glu Ser	Pro 1590 Asp Lys Thr Asp Glu 1670 Pro Lys Pro Lys Val 1750	Leu 1575 Ser Arg Ile Tyr Gly 1655 Tyr Leu Phe Asn Thr 1735 Val	1560 Gln Gly Pro Ala Ser 1640 Glu Thr Ile Thr Val 1720 Gly Val	Lys Pro Glu Lys Trp 1625 Ser Glu Val Gly Gln 1705 Gln Pro Ser	Thr Ser Gly 1610 Glu Fro Asp Ser Thr 1690 Val Leu Met Gly	Val Gln 1595 Leu Ser Glu Thr Val 1675 Gln Thr Thr Lys Leu 1755	Glu 1580 Pro Ala Pro Asp Ala 1660 Val Ser Pro Gly Glu 1740 Met	1565 Tyr Leu Phe Gln Gly 1645 Glu Ala Thr Thr Tyr 1725 Ile Val	Val Val Thr Gly 1630 Leu Ala Ser 1710 Arg Asn	Gln Val Gln Asp 1615 Gln His Gln His Leu Val Leu Thr	Thr 1600 Val Val Glu Gly Asp 1680 Pro Ser Arg Ala Lys 1760
Glu Met 1570 Val Tyr 1585 Ala Val Asp Val Ser Arg Leu Phe 1650 Leu Arg 1665 Asp Met Ala Pro Ala Gln Val Thr 1730 Pro Asp	1555 Thr Ala Thr Asp Tyr 1635 Pro Glu Thr Trp 1715 Pro) Ser Val	Gly Ile Gln Asn Ser 1620 Arg Ala Gly Ser Asp 1700 Thr Lys Ser Ser	Pro Glu Asn Ile 1605 Ile Val Pro Ser Gln 1685 Leu Pro Glu Ser Val 1765	Pro 1590 Asp Lys Thr Asp Glu 1670 Pro Lys Pro Lys Val 1750 Tyr	Leu 1575 Ser Arg Ile Tyr Gly 1655 Tyr Leu Phe Asn Thr 1735 Val	1560 Gln Gly Pro Ala Ser 1640 Glu Thr Ile Thr Val 1720 Gly Val Leu	Lys Pro Glu Lys Trp 1625 Ser Glu Val Gly Gln 1705 Gln Pro Ser Lys	Thr Thr Ser Gly 1610 Glu Fro Asp Ser Thr 1690 Val Leu Met Gly Asp 1770	Val Gln 1595 Leu Ser Glu Thr Val 1675 Gln Thr Lys Leu 1755 Thr	Glu 1580 Pro Ala Pro Asp Ala 1660 Val Ser Pro Gly Glu 1740 Met	1565 Tyr Leu Phe Gln Gly 1645 Glu Ala Thr Thr Tyr 1725 Ile Val Thr	Asp Val Val Thr Gly 1630 Leu Leu Ala Ser 1710 Arg Asn Ala Ser	Gln Val Gln Asp 1615 Gln His Gln His Leu Val Leu Thr Arg 1775	Thr 1600 Val Val Glu Gly Asp 1680 Pro Ser Arg Ala Lys 1760 Pro

1780	0	1785	1790
Ala Arg Val Thr 1795	Asp Ala Thr Glu 1800	Thr Thr Ile Thr	Ile Ser Trp Arg 1805
Thr Lys Thr Glu 1810	Thr Ile Thr Gly 1815	Phe Gln Val Asp 1820	
1825	1830	Thr Ile Lys Pro 1835	1840
Tyr Thr Ile Thr	Gly Leu Gln Pro 1845	Gly Thr Asp Tyr 1850	Lys Ile Tyr Leu 1855
Tyr Thr Leu Asn 1860		Ser Ser Pro Val 1865	Val Ile Asp Ala 1870
Ser Thr Ala Ile 1875	Asp Ala Pro Ser 1880	Asn Leu Arg Phe	Leu Ala Thr Thr 1885
1890	1895	Gln Pro Pro Arg 1900)
1905	1910	Pro Gly Ser Pro 1915	1920
	1925	Thr Glu Ala Thr 1930	1935
1940		Tyr Val Ile Ala 1945	1950
1955	1960		1965
1970	1975	Asn Leu His Gly 1980	
1985	1990	Thr Pro Phe Val 1995	2000
	2005	Leu Pro Gly Thr 2010	2015
2020)	Phe Glu Glu His 2025	2030
2035	2040		2045
2050	2055	Ala Leu Ser Gln 2060	
2065	2070	Glu Tyr Ile Ile 2075	2080
	2085	Gln Phe Arg Val 2090	2095
2100)	Thr Arg Gly Ala 2105	2110
2115	2120		2125
2130	2135	Asn Glu Gly Leu 2140	
2145	2150	Thr Val Ser His 2155	2160
	2165	Ser Gly Phe Lys 2170	2175
2180)	Phe Arg Cys Asp 2185	2190
2195	2200		2205
2210	2215	Ser Cys Thr Cys 2220	_
2225	2230	His Glu Ala Thr 2235	2240
GIY LYS INT TYT	2245	Gln Trp Gln Lys 2250	Glu Tyr Leu Gly 2255

Ala Ile Cys Ser Cys Thr Cys Phe Gly Gly Gln Arg Gly Trp Arg Cys

2260 2265 2270
Asp Asn Cys Arg Arg Pro Gly Gly Glu Pro Ser Pro Glu Gly Thr Thr

2275 2280 2285

Gly Gln Ser Tyr Asn Gln Tyr Ser Gln Arg Tyr His Gln Arg Thr Asn 2290 2295 2300

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<210> 65

<211> 1844

<212> DNA

<213> Homo sapiens

<400> 65

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<210> 66

<211> 326

<212> PRT

<213> Homo sapiens

<400> 66

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Pro Thr Ile Asn Ala Ile Thr Thr Ser Gln Asp Leu Gln Trp Met Val
                       55
Gln Pro Thr Val Ile Thr Ser Met Ser Asn Pro Tyr Pro Arg Ser His
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                                      75
Pro Tyr Ser Pro Leu Pro Gly Leu Ala Ser Val Pro Gly His Met Ala
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                                  90
Leu Pro Arg Pro Gly Val Ile Lys Thr Ile Gly Thr Thr Val Gly Arg
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Arg Arg Arg Asp Glu Gln Leu Ser Pro Glu Glu Glu Lys Arg Arg
                          120
Ile Arg Arg Glu Arg Asn Lys Leu Ala Ala Lys Cys Arg Asn Arg
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                                          140
Arg Arg Glu Leu Thr Glu Lys Leu Gln Ala Glu Thr Glu Glu Leu Glu
                   150
                                      155
Glu Glu Lys Ser Gly Leu Gln Lys Glu Ile Ala Glu Leu Gln Lys Glu
                                 170
               165
                                                     175
Lys Glu Lys Leu Glu Phe Met Leu Val Ala His Gly Pro Val Cys Lys
                             185
           180
Ile Ser Pro Glu Glu Arg Arg Ser Pro Pro Ala Pro Gly Leu Gln Pro
                          200 . 205
       195
Met Arg Ser Gly Gly Gly Ser Val Gly Ala Val Val Lys Gln Glu
                       215
                                         220
Pro Leu Glu Glu Asp Ser Pro Ser Ser Ser Ala Gly Leu Asp Lys
                   230
                                     235
Ala Gln Arg Ser Val Ile Lys Pro Ile Ser Ile Ala Gly Gly Phe Tyr
               245
                                  250
Gly Glu Glu Pro Leu His Thr Pro Ile Val Val Thr Ser Thr Pro Ala
                              265
          260
                                                  270
Val Thr Pro Gly Thr Ser Asn Leu Val Phe Thr Tyr Pro Ser Val Leu
       275
                          280
                                              285
Glu Gln Glu Ser Pro Ala Ser Pro Ser Glu Ser Cys Ser Lys Ala His
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Pro Thr Leu Leu Ala Leu
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<210> 67
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<220>

<400> 67

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<211> 3602

<212> DNA

<213> Homo sapiens

<221> misc feature

<222> 2087, 2093, 2098

<223> n = A, T, C or G

PCT/US02/18638

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Gln Ala Leu Leu Gly Cys His Ala Ser Leu Gly His Arg Leu Gly
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Ala Gly Gln Val Pro Gly Leu Thr Leu Gly Leu Thr Val Gly Ile Trp
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Ser Gly Gly Leu Cys Thr Leu Ile Tyr Ser Thr Glu Leu Lys Ala Leu
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133

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Arg Glu Ile Val Ala Leu Lys Thr Lys Leu Lys Glu Cys Glu Ala Ser
Lys Asp Gln Asn Thr Pro Val Val His Pro Pro Pro Thr Pro Gly Ser
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Cys Gly His Gly Gly Val Val Asn Ile Ser Lys Pro Ser Val Val Gln
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Tyr Ser Pro Gln His Pro Asn Lys Gly Leu Tyr Trp Val Ala Pro Leu
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Asp Asp Leu Leu Tyr Ile Asn Ala Arg Glu Leu Arg Ile Thr Tyr
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Ala Lys Gly Asp Asn Val Tyr Glu Phe His Leu Glu Phe Leu Asp Leu
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Val Lys Pro Glu Pro Val Tyr Lys Leu Thr Gln Arg Gln Val Asn Ile
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Thr Val Gln Lys Lys Val Ser Gln Trp Trp Glu Arg Leu Thr Lys Gln
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Glu Lys Arg Pro Leu Phe Leu Ala Pro Asp Phe Asp Arg Trp Leu Asp
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Glu Ser Asp Ala Glu Met Glu Leu Arg Ala Lys Glu Glu Glu Arg Leu
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Leu Arg Lys Gly Tyr Leu Phe Met Tyr Asn Leu Val Gln Phe Leu Gly
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Gly Ile Ser Arg Arg Met Pro Pro Pro Ala Asn Leu Pro Ser Leu Lys 50 55 60

Ala Glu Asn Lys Gly Asn Asp Pro Asn Val Asn Ile Val Pro Lys Asp 65 70 75 80

Gly Thr Gly Trp Ala Ser Lys Gln Glu Gln His Glu Glu Glu Lys Thr 85 90 95

Pro Glu Val Pro Pro Ala Gln Pro Lys Pro Gly Val Ala Ala Pro Pro
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Glu Val Ala Pro Ala Pro Lys Ser Trp Ala Ser Asn Lys Gln Gly Gly
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Gln Gly Asp Gly Ile Gln Val Asn Ser Gln Phe Gln Glu Phe Pro 130 135 140

Ser Leu Gln Ala Ala Gly Asp Gln Glu Lys Lys Glu Lys Glu Thr Asn 145 150 155 160

Asp Asp Asn Tyr Gly Pro Gly Pro Ser Leu Arg Pro Pro Asn Val Ala
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Cys Trp Arg Asp Gly Gly Lys Ala Ala Gly Ser Pro Ser Ser Asp 180 185 190

Gln Asp Glu Lys Leu Pro Gly Gln Asp Glu Ser Thr Ala Gly Thr Ser 195 200 205

Glu Gln Asn Asp Ile Leu Lys Val Val Glu Lys Arg Ile Ala Cys Gly
210 215 220

Pro Pro Gln Ala Lys Leu Asn Gly Gln Gln Ala Ala Leu Ala Ser Gln 225 230 235

Tyr Arg Ala Met Met Pro Pro Tyr Met Phe Gln Gln Tyr Pro Arg Met 245 250 255

Thr Tyr Pro Pro Leu His Gly Pro Met Arg Phe Pro Pro Ser Leu Ser 260 265 270

Glu Thr Asn Lys Gly Leu Arg Gly Arg Gly Pro Pro Pro Ser Trp Ala 275 280 285

Ser	Glu 290	Pro	Glu	Arg	Pro	Ser 295	Ile	Leu	Ser	Ala	Ser 300	Glu	Leu	Lys	Glu
Leu 305	Asp	Lys	Phe	Asp	Asn 310	Leu	Asp	Ala	Glu	Ala 315	Asp	Glu	Gly	Trp	Ala 320
Gly	Ala	Gln	Met	Glu 325	Val	Asp	Tyr	Thr	Glu 330	Gln	Leu	Asn	Phe	Ser 335	Asp
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Gly	Thr	Ser	Ser	His 405	Leu	Pro	Pro	Pro	Pro 410	Lys	Leu	Leu	Ala	Gln 415	Gln
			420					425			_		430	Pro	
		435					440					445		Gln	-
	450					455					460	_		Arg	_
465					470					475				Ala	480
				485					490	_		_		Leu 495	
			500					505				-	510	Lys	
		515					520					525		Arg	
	530					535					540	_		Lys -	
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				565					570					Lys 575	
			580					585					590	Lys Leu	
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		675					680					685		Gln	
	690					695					700			Gln	
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				725					730					735 Gly	
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760 Pro Leu Met Arg Arg Asp Gln Met Glu Gly Ser Pro Asn Ser Ser Glu 770 775 780 Ser Phe Glu His Ile Ala Arg Ser Ala Arg Asp His Ala Ile Ser Leu 790 795 Ser Glu Pro Arg Met Leu Trp Gly Ser Asp Pro Tyr Pro His Ala Glu 805 810 Pro Gln Gln Ala Thr Thr Pro Lys Ala Thr Glu Glu Pro Glu Asp Val 820 825 Arg Ser Glu Ala Ala Leu Asp Gln Glu Gln Ile Thr Ala Ala Tyr Ser 835 840 Val Glu His Asn Gln Leu Glu Ala His Pro Lys Ala Asp Phe Ile Arg 850 855 860 Glu Ser Ser Glu Ala Gln Val Gln Lys Phe Leu Ser Arg Ser Val Glu 870 875 Asp Val Arg Pro His His Thr Asp Ala Asn Asn Gln Ser Ala Cys Phe 885 890 895 Glu Ala Pro Asp Gln Lys Thr Leu Ser Ala Pro Gln Glu Glu Arg Ile 900 905 910 Ser Ala Val Glu Ser Gln Pro Ser Arg Lys Arg Ser Val Ser His Gly 915 920 925 Ser Asn His Thr Gln Lys Pro Asp Glu Gln Arg Ser Glu Pro Ser Ala 930 935 940 Gly Ile Pro Lys Val Thr Ser Arg Cys Ile Asp Ser Lys Glu Pro Ile 945 950 955 960 Glu Arg Pro Glu Glu Lys Pro Lys Lys Glu Gly Phe Ile Arg Ser Ser 965 970 Glu Gly Pro Lys Pro Glu Lys Val Tyr Lys Ser Lys Ser Glu Thr Arg 980 985 990 Trp Gly Pro Arg Pro Ser Ser Asn Arg Arg Glu Glu Val Asn Asp Arg 995 1000 1005 Pro Val Arg Arg Ser Gly Pro Ile Lys Lys Pro Val Leu Arg Asp Met 1010 1015 1020 Lys Glu Glu Arg Glu Gln Arg Lys Glu Lys Glu Gly Glu Lys Ala Glu 1025 1030 1035 1040 Lys Val Thr Glu Lys Val Val Lys Pro Glu Lys Thr Glu Lys Lys 1045 1050 1055 Asp Leu Pro Pro Pro Pro Pro Pro Gln Pro Pro Ala Pro Ile Gln 1060 1065 1070 Pro Gln Ser Val Pro Pro Pro Ile Gln Pro Glu Ala Glu Lys Phe Pro 1075 1080 1085 Ser Thr Glu Thr Ala Thr Leu Ala Gln Lys Pro Ser Gln Asp Thr Glu 1090 1095 1100 Lys Pro Leu Glu Pro Val Ser Thr Val Gln Val Glu Pro Ala Val Lys 1110 1115 Thr Val Asn Gln Gln Thr Met Ala Ala Pro Val Val Lys Glu Glu Lys 1125 1130 Gln Pro Glu Lys Val Ile Ser Lys Asp Leu Val Ile Glu Arg Pro Arg 1140 1145 1150 Pro Asp Ser Arg Pro Ala Val Lys Lys Glu Ser Thr Leu Pro Pro Arg 1155 1160 1165 Thr Tyr Trp Lys Glu Ala Arg Glu Arg Asp Trp Phe Pro Asp Gln Gly 1170 1175 1180 Tyr Arg Gly Arg Gly Arg Gly Glu Tyr Tyr Ser Arg Gly Arg Ser Tyr 1185 1190 1195 1200 Arg Gly Ser Tyr Gly Gly Arg Gly Arg Gly Arg Gly His Thr Arg 1205 1210 1215 Asp Tyr Pro Gln Tyr Arg Asp Asn Lys Pro Arg Ala Glu His Ile Pro

1225

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Ser Asp Phe Glu 1250		1255	•			1260)			
Thr Asp Thr Asp 1265	127	0			1275	<u>;</u>				1280
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Ile Asp Asn Arg 1315	Leu Leu		Lys Pro	Tyr	Val	Arg	Asp 1325		Asp	Lys
Ala Lys Pro Gly 1330	Phe Leu	Pro 1335		Glu	Pro	Thr 1340	_	Arg	Gly	Arg
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Arg Pro Ser Thr	1365			1370)				1375	5
Pro Arg Gln Ser 138	0		138	5				1390)	
Arg His Glu Gln 1395			1400				1405	5		
Phe Glu Arg Lys 1410		1415				1420)			
Pro Thr Arg Pro 1425	Pro Arg 143		Asp Lys	Pro	Pro 1435		Phe	Arg	Arg	Leu 1440
Arg Glu Arg Glu	Ala Ala 1445	Ser	Lys Ser	Asn 1450		Val	Val	Ala	Val 1455	
Thr Asn Gly Thr		Asn			Glu	Pro	Val	Asn	Thr	Leu
146			146					1470		
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1905	5				1910)				Ala 1915	5				1920
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	2050)				2055	ō			Pro	2060)			
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				2085	š				2090				_	2095	5
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Cys Ser Pro Ala Thr Ala Arg Val Cys Ala Leu Gly His Arg Gln Trp
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Glu Thr Leu Gly Arg Ser Asp Pro Ala Pro Tyr Pro Cys Leu Pro Val
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Pro Glu Cys Leu Leu Arg Val Leu Ala Gly Gly Leu Arg Arg Ala His
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<213> Homo sapiens

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125

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<211> 3103

<212> DNA

<213> Homo sapiens

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<212> PRT

<213> Homo sapiens

<400> 107

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			180					185				Ile	190	_	
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<211> 2620 <212> DNA

<213> Homo sapiens

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Val Asn Ala Ala Arg Ala Lys Phe Arg Thr Val Ala Ile Ile Ala Arg
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Gln Ile Ser Asp Glu Val Ala Glu Arg Leu Met Thr Ile Ala Tyr Glu
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Ser Gly Val Asn Leu Phe Asp Thr Ala Glu Val Tyr Ala Ala Gly Lys
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Ala Glu Val Ile Leu Gly Ser Ile Ile Lys Lys Lys Gly Trp Arg Arg
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Ser Ser Leu Val Ile Thr Thr Lys Leu Tyr Trp Gly Gly Lys Ala Glu
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                               170
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Gly Ala Ile Gln Val Leu Pro Lys Met Thr Ser His Val Val Asn Glu
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<400> 110

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<212> DNA

<213> Homo sapiens

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Val Tyr Val Ile Asn Lys Glu Ile Cys Val Arg Thr Val Cys Ala His
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Glu Glu Leu Leu Arg Ala Asp Leu Cys Arg Asp Lys Phe Ser Lys Cys
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192

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Val Tyr Thr Ser Gly Lys Ala Ser Ser Ala Ala Gly Leu Thr Ala Ala 420 425 Val Val Arg Asp Glu Glu Ser His Glu Phe Val Ile Glu Ala Gly Ala 440 Leu Met Leu Ala Asp Asn Gly Val Cys Cys Ile Asp Glu Phe Asp Lys 455 460 Met Asp Val Arg Asp Gln Val Ala Ile His Glu Ala Met Glu Gln Gln 470 475 Thr Ile Ser Ile Thr Lys Ala Gly Val Lys Ala Thr Leu Asn Ala Arg , 485 490 Thr Ser Ile Leu Ala Ala Ala Asn Pro Ile Ser Gly His Tyr Asp Arg 500 505 Ser Lys Ser Leu Lys Gln Asn Ile Asn Leu Ser Ala Pro Ile Met Ser 520 Arg Phe Asp Leu Phe Phe Ile Leu Val Asp Glu Cys Asn Glu Val Thr 535 Asp Tyr Ala Ile Ala Arg Arg Ile Val Asp Leu His Ser Arg Ile Glu 550 555 Glu Ser Ile Asp Arg Val Tyr Ser Leu Asp Asp Ile Arg Arg Tyr Leu 565 570 575 Leu Phe Ala Arg Gln Phe Lys Pro Lys Ile Ser Lys Glu Ser Glu Asp 585 580 Phe Ile Val Glu Gln Tyr Lys His Leu Arg Gln Arg Asp Gly Ser Gly 600 Val Thr Lys Ser Ser Trp Arg Ile Thr Val Arg Gln Leu Glu Ser Met 610 615 620 Ile Arg Leu Ser Glu Ala Met Ala Arg Met His Cys Cys Asp Glu Val 625 630 635 Gln Pro Lys His Val Lys Glu Ala Phe Arg Leu Leu Asn Lys Ser Ile 645 650 Ile Arg Val Glu Thr Pro Asp Val Asn Leu Asp Gln Glu Glu Ile 660 665 Gln Met Glu Val Asp Glu Gly Ala Gly Gly Ile Asn Gly His Ala Asp 680 685 Ser Pro Ala Pro Val Asn Gly Ile Asn Gly Tyr Asn Glu Asp Ile Asn 695 700 Gln Glu Ser Ala Pro Lys Ala Ser Leu Arg Leu Gly Phe Ser Glu Tyr 705 710 715 Cys Arg Ile Ser Asn Leu Ile Val Leu His Leu Arg Lys Val Glu Glu 725 730 Glu Glu Asp Glu Ser Ala Leu Lys Arg Ser Glu Leu Val Asn Trp Tyr 745 750 740 Leu Lys Glu Ile Glu Ser Glu Ile Asp Ser Glu Glu Glu Leu Ile Asn 755 760 765 Lys Lys Arg Ile Ile Glu Lys Val Ile His Arg Leu Thr His Tyr Asp 770 775 780 His Val Leu Ile Glu Leu Thr Gln Ala Gly Leu Lys Gly Ser Thr Glu 790 795 Gly Ser Glu Ser Tyr Glu Glu Asp Pro Tyr Leu Val Val Asn Pro Asn 805 810 Tyr Leu Leu Glu Asp

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                                                    30
Pro Gly Ser Glu Cys Ala Glu Trp Ala Trp Gly Pro Cys Thr Pro Ser
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Ser Lys Asp Cys Gly Val Gly Phe Arg Glu Gly Thr Cys Gly Ala Gln
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Thr Gln Arg Ile Arg Cys Arg Val Pro Cys Asn Trp Lys Lys Glu Phe
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Gly Ala Asp Cys Lys Tyr Lys Phe Glu Asn Trp Gly Ala Cys Asp Gly
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Gly Thr Gly Thr Lys Val Arg Gln Gly Thr Leu Lys Lys Ala Arg Tyr
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Arg Trp Arg Ala Lys Val Gln Glu Arg Ile Arg Glu Arg Ser Lys Pro
                        55
Val His Glu Leu Asn Arg Glu Ala Cys Asp Asp Tyr Arg Leu Cys Glu
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WO 02/101075 PCT/US02/18638 199

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203

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1-				Val	Thr	Gly		Leu						Lys	Met
Leu	610	Ala	Gln		Arg		Ala	Leu	Arg	Ser Phe	Gly 620	Arg	Gly	_	Gln
Leu 625	610 Leu	Ala Phe	Gln Ser	Gly Arg	Arg 630	Gly 615	Ala Leu	Leu Trp	Arg Arg Val	Ser Phe 635	Gly 620 Asp	Arg Val	Gly Lys	Ala Pro	Gln 640
Leu 625 Met	610 Leu Val	Ala Phe Asp	Gln Ser Pro Asp	Gly Arg 645	Arg 630 Ser	Gly 615 Arg	Ala Leu Ser	Leu Trp Glu Phe	Arg Arg Val 650	Ser Phe 635 Asp	Gly 620 Asp Arg	Arg Val Met	Gly Lys Phe Lys	Ala Pro 655	Gln 640 Gly
Leu 625 Met Val	610 Leu Val Pro	Ala Phe Asp Leu Gln	Ser Pro Asp 660	Gly Arg 645 Thr	Arg 630 Ser His	Gly 615 Arg Ala Asp	Ala Leu Ser Val	Leu Trp Glu Phe 665	Arg Arg Val 650 Gln	Ser Phe 635 Asp Tyr	Gly 620 Asp Arg	Arg Val Met Glu Arg	Gly Lys Phe Lys 670	Ala Pro 655 Ala	Gln 640 Gly Tyr
Leu 625 Met Val Phe	610 Leu Val Pro Cys Gln	Ala Phe Asp Leu Gln 675	Ser Pro Asp 660 Asp	Gly Arg 645 Thr Arg	Arg 630 Ser His Phe	Gly 615 Arg Ala Asp Tyr Gly	Ala Leu Ser Val Trp	Trp Glu Phe 665 Arg	Arg Val 650 Gln Val	Ser Phe 635 Asp Tyr Ser	Gly 620 Asp Arg Arg Ser Asp	Arg Val Met Glu Arg 685	Gly Lys Phe Lys 670 Ser	Ala Pro 655 Ala Glu	Gln 640 Gly Tyr Leu
Leu 625 Met Val Phe Asn	610 Leu Val Pro Cys	Ala Phe Asp Leu Gln 675 Val	Ser Pro Asp 660 Asp	Gly Arg 645 Thr Arg	Arg 630 Ser His Phe	Gly 615 Arg Ala Asp	Ala Leu Ser Val Trp	Trp Glu Phe 665 Arg	Arg Val 650 Gln Val	Ser Phe 635 Asp Tyr Ser	Gly 620 Asp Arg Arg	Arg Val Met Glu Arg 685	Gly Lys Phe Lys 670 Ser	Ala Pro 655 Ala Glu	Gln 640 Gly Tyr Leu

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Gln Leu Leu Gly Phe Pro Cys Ala Glu Val Ser Gly Leu Ser Thr Glu

Arg Val Arg Glu Leu Ala Val Ala Leu Ala Gln Lys Asn Val Lys Leu 90 Ser Thr Glu Gln Leu Arg Cys Leu Ala His Arg Leu Ser Glu Pro Pro 105 Glu Asp Leu Asp Ala Leu Pro Leu Asp Leu Leu Phe Leu Asn Pro 120 Asp Ala Phe Ser Gly Pro Gln Ala Cys Thr Arg Phe Phe Ser Arg Ile 135 Thr Lys Ala Asn Val Asp Leu Leu Pro Arg Gly Ala Pro Glu Arg Gln 150 155 Arg Leu Leu Pro Ala Ala Leu Ala Cys Trp Gly Val Arg Gly Ser Leu 165 170 Leu Ser Glu Ala Asp Val Arg Ala Leu Gly Gly Leu Ala Cys Asp Leu 185 Pro Gly Arg Phe Val Ala Glu Ser Ala Glu Val Leu Leu Pro Arg Leu 200 Val Ser Cys Pro Gly Pro Leu Asp Gln Asp Gln Gln Glu Ala Ala Arg 215 220 Ala Ala Leu Gln Gly Gly Pro Pro Tyr Gly Pro Pro Ser Thr Trp 230 235 Ser Val Ser Thr Met Asp Ala Leu Arg Gly Leu Leu Pro Val Leu Gly 245 250 255 Gln Pro Ile Ile Arg Ser Ile Pro Gln Gly Ile Val Ala Ala Trp Arg 260 265 Gln Arg Ser Ser Arg Asp Pro Ser Trp Arg Gln Pro Glu Arg Thr Ile 275 280 Leu Arg Pro Arg Phe Arg Arg Glu Val Glu Lys Thr Ala Cys Pro Ser 295 300 Gly Lys Lys Ala Arg Glu Ile Asp Glu Ser Leu Ile Phe Tyr Lys Lys 310 315 Trp Glu Leu Glu Ala Cys Val Asp Ala Ala Leu Leu Ala Thr Gln Met 325 330 335 Asp Arg Val Asn Ala Ile Pro Phe Thr Tyr Glu Gln Leu Asp Val Leu 345 350 Lys His Lys Leu Asp Glu Leu Tyr Pro Gln Gly Tyr Pro Glu Ser Val 355 360 365 Ile Gln His Leu Gly Tyr Leu Phe Leu Lys Met Ser Pro Glu Asp Ile 375 380 Arg Lys Trp Asn Val Thr Ser Leu Glu Thr Leu Lys Ala Leu Leu Glu 390 395 Val Asn Lys Gly His Glu Met Ser Pro Gln Ala Pro Arg Pro Leu 405 410 Pro Gln Val Ala Thr Leu Ile Asp Arg Phe Val Lys Gly Arg Gly Gln 420 425 Leu Asp Lys Asp Thr Leu Asp Thr Leu Thr Ala Phe Tyr Pro Gly Tyr 440 Leu Cys Ser Leu Ser Pro Glu Glu Leu Ser Ser Val Pro Pro Ser Ser 455 Ile Trp Ala Val Arg Pro Gln Asp Leu Asp Thr Cys Asp Pro Arg Gln 470 475 Leu Asp Val Leu Tyr Pro Lys Ala Arg Leu Ala Phe Gln Asn Met Asn 485 490 Gly Ser Glu Tyr Phe Val Lys Ile Gln Ser Phe Leu Gly Gly Ala Pro 500 505 Thr Glu Asp Leu Lys Ala Leu Ser Gln Gln Asn Val Ser Met Asp Leu 520 Ala Thr Phe Met Lys Leu Arg Thr Asp Ala Val Leu Pro Leu Thr Val 535 Ala Glu Val Gln Lys Leu Leu Gly Pro His Val Glu Gly Leu Lys Ala

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545
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Glu Glu Arg His Arg Pro Val Arg Asp Trp Ile Leu Arg Gln Arg Gln
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Asp Asp Leu Asp Thr Leu Gly Leu Gly Leu Gln Gly Gly Ile Pro Asn
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                                                     590
Gly Tyr Leu Val Leu Asp Leu Ser Val Gln Gly Gly Arg Gly Gln
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Ala Arg Ala Gly Gly Arg Ala Gly Gly Val Glu Val Gly Ala Leu Ser
                        615
                                             620
His Pro Ser Leu Cys Arg Gly Pro Leu Gly Asp Ala Leu Pro Pro Arg
                    630
                                         635
Thr Trp Thr Cys Ser His Arg Pro Gly Thr Ala Pro Ser Leu His Pro
                645
                                    650
Gly Leu Arg Ala Pro Leu Pro Cys Trp Pro Gln Pro Cys Trp Gly Ser
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Pro Pro Gly Gln Glu Gln Ala Arg Val Ile Pro Val Pro Pro Gln Glu
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<210> 145 <211> 2135 <212> DNA <213> Homo sapiens

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ctaggacctg gacctgttct caccgtcctg gcactgctcc tagcctccac cctggcctga 1980 gggccccact cccttgctgg ccccagccct gctggggatc cccgcctggc caggagcagg 2040 cacgggtgat ccccgttcca ccccaagaga actcgcgctc agtaaacggg aacatgcccc 2100 ctgcagacac gtaaaaaaaa aaaaaaaaa aaaaa

<210> 146 <211> 630 <212> PRT <213> Home

<213> Homo sapiens

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Arg Lys Trp Asn Val Thr Ser Leu Glu Thr Leu Lys Ala Leu Leu Glu
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Val Asn Lys Gly His Glu Met Ser Pro Gln Ala Pro Arg Pro Leu
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                                                         415
Pro Gln Val Ala Thr Leu Ile Asp Arg Phe Val Lys Gly Arg Gly Gln
            420
                                425
Leu Asp Lys Asp Thr Leu Asp Thr Leu Thr Ala Phe Tyr Pro Gly Tyr
        435
                            440
                                                 445
Leu Cys Ser Leu Ser Pro Glu Glu Leu Ser Ser Val Pro Pro Ser Ser
                        455
                                            460
Ile Trp Ala Val Arg Pro Gln Asp Leu Asp Thr Cys Asp Pro Arg Gln
                    470
                                        475
Leu Asp Val Leu Tyr Pro Lys Ala Arg Leu Ala Phe Gln Asn Met Asn
                485
                                    490
                                                         495
Gly Ser Glu Tyr Phe Val Lys Ile Gln Ser Phe Leu Gly Gly Ala Pro
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                                                     510
Thr Glu Asp Leu Lys Ala Leu Ser Gln Gln Asn Val Ser Met Asp Leu
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                                                525
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Ala Thr Phe Met Lys Leu Arg Thr Asp Ala Val Leu Pro Leu Thr Val
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                                            540
Ala Glu Val Gln Lys Leu Gly Pro His Val Glu Gly Leu Lys Ala
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                                        555
Glu Glu Arg His Arg Pro Val Arg Asp Trp Ile Leu Arg Gln Arg Gln
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                                                        575
Asp Asp Leu Asp Thr Leu Gly Leu Gly Leu Gln Gly Gly Ile Pro Asn
                                585
                                                    590
Gly Tyr Leu Val Leu Asp Leu Ser Val Gln Glu Ala Leu Ser Gly Thr
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Pro Cys Leu Leu Gly Pro Gly Pro Val Leu Thr Val Leu Ala Leu Leu
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Leu Ala Ser Thr Leu Ala
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<213> Homo sapiens

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<210> 148

<211> 620

<212> PRT

<213> Homo sapiens

<400> 148

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210

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Trp Glu Leu Glu Ala Cys Val Asp Ala Ala Leu Leu Ala Thr Gln Met
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Asp Arg Val Asn Ala Ile Pro Phe Thr Tyr Glu Gln Leu Asp Val Leu
                               345
Lys His Lys Leu Asp Glu Leu Tyr Pro Gln Gly Tyr Pro Glu Ser Val
                            360
Ile Gln His Leu Gly Tyr Leu Phe Leu Lys Met Ser Pro Glu Asp Ile
                        375
Arg Lys Trp Asn Val Thr Ser Leu Glu Thr Leu Lys Ala Leu Leu Glu
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                                       395
Val Asn Lys Gly His Glu Met Ser Pro Gln Ala Pro Arg Arg Pro Leu
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                                   410
Pro Gln Val Ala Thr Leu Ile Asp Arg Phe Val Lys Gly Arg Gly Gln
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                                                   430
Leu Asp Lys Asp Thr Leu Asp Thr Leu Thr Ala Phe Tyr Pro Gly Tyr
                           440
                                               445
       435
Leu Cys Ser Leu Ser Pro Glu Glu Leu Ser Ser Val Pro Pro Ser Ser
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Ile Trp Ala Val Arg Pro Gln Asp Leu Asp Thr Cys Asp Pro Arg Gln
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                   470
Leu Asp Val Leu Tyr Pro Lys Ala Arg Leu Ala Phe Gln Asn Met Asn
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Gly Ser Glu Tyr Phe Val Lys Ile Gln Ser Phe Leu Gly Gly Ala Pro
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                                                   510
Thr Glu Asp Leu Lys Ala Leu Ser Gln Gln Asn Val Ser Met Asp Leu
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Ala Thr Phe Met Lys Leu Arg Thr Asp Ala Val Leu Pro Leu Thr Val
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                                           540
Ala Glu Val Gln Lys Leu Gly Pro His Val Glu Gly Leu Lys Ala
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                                       555
Glu Glu Arg His Arg Pro Val Arg Asp Trp Ile Leu Arg Gln Arg Gln
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                                   570
Asp Asp Leu Asp Thr Leu Gly Leu Gly Leu Gln Gly Gly Ile Pro Asn
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<210> 149

<211> 2193

<212> DNA

<213> Homo sapiens

<400> 149

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213

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<213> Homo sapiens

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375 . 380

410

395

Met Gly Ile Asn Val Thr Asp Phe Thr Arg Ser Ile Leu Thr Pro Arg

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390

405

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Gln Ala		900					905					910		_
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Arg Lys 945	Lys	Met	Ala	Gln 950	Gln	Met	Leu	Asp	Leu 955	Glu	Glu	Gln	Leu	Glu 960
Glu Glu	Glu .	Ala	Ala 965	Arg	Gln	Lys	Leu	Gln 970	Leu	Glu	Lys	Val	Thr 975	Ala
Glu Ala		Ile 980	Lys	Lys	Leu	Glu	Asp 985	Glu	Ile	Leu	Val	Met 990	Asp	Asp
Gln Asn	Asn 995	Lys	Leu	Ser	Lys	Glu 1000		Lys	Leu	Leu	Glu 1005		Arg	Ile
Ser Asp		Thr	Thr	Asn	Leu 1015		Glu	Glu	Glu	Glu 1020		Ala	Lys	Asn
Leu Thr 1025	Lys	Leu	Lys	Asn 1030		His	Glu	Ser	Met 1035		Ser	Glu	Leu	Glu 1040
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Lys Arg		Leu 1060		Gly	Asp	Ala	Ser 1065		Phe	His	Glu	Gln 1070		Ala
Asp Leu	Gln 1075		Gln	Ile	Ala	Glu 1080		Lys	Met	Gln	Leu 1085		Lys	Lys
Glu Glu 109		Leu	Gln	Ala	Ala 1095		Ala	Arg	Leu	Asp 1100		Glu	Ile	Ala
Gln Lys 1105	Asn .	Asn	Ala	Leu 1110		Lys	Ile	Arg	Glu 1115		Glu	Gly	His	Ile 1120
Ser Asp	Leu	Gln	Glu 1125		Leu	Asp	Ser	Glu 1130		Ala	Ala	Arg	Asn 1135	
Ala Glu		Gln 1140		Arg	Asp	Leu	Gly 1145		Glu	Leu	Glu	Ala 1150		Lys
Thr Glu	Leu 1155		Asp	Thr	Leu	Asp 1160		Thr	Ala	Thr	Gln 1165		Glu	Leu
Arg Ala 117		Arg	Glu	Gln	Glu 1175		Thr	Val	Leu	Lys 1180		Ala	Leu	Asp
Glu Glu 1185	Thr .	Arg	Ser	His 1190		Ala	Gln	Val	Gln 1195		Met	Arg	Gln	Lys 1200
His Ala	Gln .	Ala	Val 1205		Glu	Leu	Thr	Glu 1210		Leu	Glu	Gln	Phe 1215	_
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Glu Val 125		His	Lys	Lys	Lys 1255		Leu	Glu	Ala	Gln 1260		Gln	Glu	Leu
Gln Ser 1265	Lys	Cys	Ser	Asp 1270	_	Glu	Arg	Ala	Arg 1275		Glu	Leu	Asn	Asp 1280
Lys Val	His :	Lys	Leu 1285		Asn	Glu	Val	Glu 1290		Val	Thr	Gly	Met 1295	
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Leu Ser	Ser 1315		Leu	Gln	Asp	Thr 1320		Glu	Leu	Leu	Gln 1325	Glu		Thr
Arg Gln 133	Lys :		Asn	Val	Ser 1335	Thr		Leu	Arg	Glń 1340	Leu		Glu	Glu
Arg Asn 1345		Leu	Gln	Asp 1350		Leu	Asp	Glu	Glu 1355	Met		Ala	Lys	Gln 1360

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1830 1835 Thr Lys Ser Leu Lys Gln Lys Asp Lys Lys Leu Lys Glu Ile Leu Leu 1845 1850 Gln Val Glu Asp Glu Arg Lys Met Ala Glu Gln Tyr Lys Glu Gln Ala 1865 1870 Glu Lys Gly Asn Ala Arg Val Lys Gln Leu Lys Arg Gln Leu Glu Glu 1.880 1885 Ala Glu Glu Glu Ser Gln Arg Ile Asn Ala Asn Arg Arg Lys Leu Gln 1895 1900 Arg Glu Leu Asp Glu Ala Thr Glu Ser Asn Glu Ala Met Gly Arg Glu 1905 1910 1915 Val Asn Ala Leu Lys Ser Lys Leu Arg Arg Gly Asn Glu Thr Ser Phe 1925 1930 Val Pro Ser Arg Arg Ser Gly Gly Arg Arg Val Ile Glu Asn Ala Asp 1940 1945 Gly Ser Glu Glu Glu Thr Asp Thr Arg Asp Ala Asp Phe Asn Gly Thr 1955 1960 Lys Ala Ser Glu 1970

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	1010)		Thr		1015	5				1020) _		_	
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	Glu 1410) .				1415	5				1420)			
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<213> Homo sapiens

<400> 165

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tgtcagagct cttcatgtcc tctttccagt cctacggagc cccacggggg gacaaggagg 720
agotgacaco coagaagtgo totgaacooo aatootoaaa atgaagatao tgacacoaco 780
tttgccctcc ccgtcaccgc gcacccaccc tgacccctcc ctcagctgtc ctgtgccccg 840
ccctetcccg cacactcagt ccccetgcct ggcgttcctg ccgcagctct gacctggtgc 900
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<210> 166
<211> 234
<212> PRT
<213> Homo sapiens
<400> 166
Met Cys Phe Pro Lys Val Leu Ser Asp Asp Met Lys Lys Leu Lys Ala
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Arg Met Val Met Leu Leu Pro Thr Ser Ala Gln Gly Leu Gly Ala Trp
                                25
Val Ser Ala Cys Asp Thr Glu Asp Thr Val Gly His Leu Gly Pro Trp
                            40
Arg Asp Lys Asp Pro Ala Leu Trp Cys Gln Leu Cys Leu Ser Ser Gln
                        55
His Gln Ala Ile Glu Arg Phe Tyr Asp Lys Met Gln Asn Ala Glu Ser
                    70
Gly Arg Gly Gln Val Met Ser Ser Leu Ala Glu Leu Glu Asp Asp Phe
Lys Glu Gly Tyr Leu Glu Thr Val Ala Ala Tyr Tyr Glu Glu Gln His
                                105
Pro Glu Leu Thr Pro Leu Leu Glu Lys Glu Arg Asp Gly Leu Arg Cys
                            120
                                                125
Arg Gly Asn Arg Ser Pro Val Pro Asp Val Glu Asp Pro Ala Thr Glu
                        135
                                            140
Glu Pro Gly Glu Ser Phe Cys Asx Lys Val Met Arg Trp Phe Gln Ala
                                        155
Met Leu Gln Arg Leu Gln Thr Trp Trp His Gly Val Leu Ala Trp Val
                                    170
Lys Glu Lys Val Val Ala Leu Val His Ala Val Gln Ala Leu Trp Lys
                                185
Gln Phe Gln Ser Phe Cys Cys Ser Leu Ser Glu Leu Phe Met Ser Ser
                            200
Phe Gln Ser Tyr Gly Ala Pro Arg Gly Asp Lys Glu Glu Leu Thr Pro
                        215
                                            220
Gln Lys Cys Ser Glu Pro Gln Ser Ser Lys
                    230
<210> 167
<211> 958
<212> DNA
<213> Homo sapiens
<400> 167
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tectecetae ttetgeteag gggttggggg cetgggtete agegtgtgae aetgaggaea 180
ctgtgggaca cctggggaccc tggagggaca aggatccggc cctttggtgc caactctgcc 240
tctcttcaca gcaccaggcc atagaaagat tttatgataa aatgcaaaat gcagaatcag 300
gacgtggaca ggtgatgtcg agcctggcag agctggagga cgacttcaaa gagggctacc 360
tggagacagt ggcggcttat tatgaggagc agcacccaga gctcactcct ctacttgaaa 420
aagaaagaga tggattacgg tgccgaggca acagatcccc tgtcccggat gttgaggatc 480
ccgcaaccga qqaqcctggg gagagctttt gtgacaaggt catqaqatqg ttccaggcca 540
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tgctgcagcg gctgcagacc tggtggcacg gggttctggc ctgggtgaag gagaaggtgg 600
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agetgacace ecagaagtge tetgaacece aateeteaaa atgaagatae tgacaceace 780
tttgccctcc ccgtcaccgc gcacccaccc tgacccctcc ctcagctgtc ctgtgccccg 840
eceteteeeg cacacteagt ecceetgeet ggegtteetg eegeagetet gacetggtge 900
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<210> 168
<211> 234
<212> PRT
<213> Homo sapiens
<400> 168
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Arg Met Val Met Leu Pro Thr Ser Ala Gln Gly Leu Gly Ala Trp
           20
                             25
Val Ser Ala Cys Asp Thr Glu Asp Thr Val Gly His Leu Gly Pro Trp
                         40
Arg Asp Lys Asp Pro Ala Leu Trp Cys Gln Leu Cys Leu Ser Ser Gln
                     55
                                        60
His Gln Ala Ile Glu Arg Phe Tyr Asp Lys Met Gln Asn Ala Glu Ser
                  70
                                    75
Gly Arg Gly Gln Val Met Ser Ser Leu Ala Glu Leu Glu Asp Asp Phe
              85
                                 90
Lys Glu Gly Tyr Leu Glu Thr Val Ala Ala Tyr Tyr Glu Glu Gln His
           100
                             105
                                               110
Pro Glu Leu Thr Pro Leu Leu Glu Lys Glu Arg Asp Gly Leu Arg Cys
                         120
                                           125
Arg Gly Asn Arg Ser Pro Val Pro Asp Val Glu Asp Pro Ala Thr Glu
                     135
                                        140
Glu Pro Gly Glu Ser Phe Cys Asp Lys Val Met Arg Trp Phe Gln Ala
                  150
                                    155
Met Leu Gln Arg Leu Gln Thr Trp Trp His Gly Val Leu Ala Trp Val
              165
                                 170
Lys Glu Lys Val Val Ala Leu Val His Ala Val Gln Ala Leu Trp Lys
           180
                             185
Gln Phe Gln Ser Phe Cys Cys Ser Leu Ser Glu Leu Phe Met Ser Ser
                         200
Phe Gln Ser Tyr Gly Ala Pro Arg Gly Asp Lys Glu Glu Leu Thr Pro
                      215
Gln Lys Cys Ser Glu Pro Gln Ser Ser Lys
225
                  230
<210> 169
<211> 1005
<212> DNA
<213> Homo sapiens
<400> 169
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gctgataaat agtttatacc caccaggaca agagcccata cccaaqatct cagagtcaaa 300
gatggctttt aagcagatgg agcaaatctc ccagttccta aaagctgcgg agacctatgg 360
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<210> 170 <211> 282 <212> PRT

<213> Homo sapiens

<400> 170

Met Ala Asn Arg Gly Pro Ser Tyr Gly Leu Ser Arg Glu Val Gln Glu Lys Ile Glu Gln Lys Tyr Asp Ala Asp Leu Glu Asn Lys Leu Val Asp 25 Trp Ile Ile Leu Gln Cys Ala Glu Asp Ile Glu His Pro Pro Pro Gly 40 Arg Ala His Phe Gln Lys Trp Leu Met Asp Gly Thr Val Leu Cys Lys 55 Leu Ile Asn Ser Leu Tyr Pro Pro Gly Gln Glu Pro Ile Pro Lys Ile 75 Ser Glu Ser Lys Met Ala Phe Lys Gln Met Glu Gln Ile Ser Gln Phe 85 90 Leu Lys Ala Ala Glu Thr Tyr Gly Val Arg Thr Thr Asp Ile Phe Gln 105 Thr Val Asp Leu Trp Glu Gly Lys Asp Met Ala Ala Val Gln Arg Thr 120 125 Leu Met Ala Leu Gly Ser Val Ala Val Thr Lys Asp Asp Gly Cys Tyr 135 140 Arg Gly Glu Pro Ser Trp Phe His Arg Lys Ala Gln Gln Asn Arg Arg 150 155 Gly Phe Ser Glu Glu Gln Leu Arg Gln Gly Gln Asn Val Ile Gly Leu 165 170 Gln Met Gly Ser Asn Lys Gly Ala Ser Gln Ala Gly Met Thr Gly Tyr 185 Gly Met Pro Arg Gln Ile Met Leu Gly Arg Gly Ile Leu Pro Leu Val 195 200 205 Glu Arg Thr Asn Val Pro His His Gly Leu Tyr Glu Lys Glu Ile Val 215 220 Ser His Leu Leu Thr Phe Ser Ser Phe Ser Lys Pro Ser Val Pro Gly 230 235 Phe Cys Lys Cys Cys Ile Ser Ala Glu Asn Pro Arg Cys Leu Leu 245 250 Pro Pro Pro Val His Leu Glu Leu Cys Lys Asp Ser Ala Ser Val Phe 265 Leu Ser Ser Ser Gly Pro Arg Val Ser Val 280

<210> 171

<211> 942

<212> DNA

<213> Homo sapiens

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<400> 171
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gccacatggc taaaccctga cccatctcag aagcagaatc tcctagcccc acagaatgct 180
gtgtcctctg aagaaaccaa tgactttaaa caagagaccc ttccaagtaa gtccaacgaa 240
agccatgacc acatggatga tatggatgat gaagatgatg atgaccatgt ggacagccag 300
gactccattg actcgaacga ctctgatgat gtagatgaca ctgatgattc tcaccagtct 360
gatgagtctc accattctga tgaatctgat gaactggtca ctgattttcc cacggacctg 420
ccagcaaccg aagttttcac tccagttgtc cccacagtag acacatatga tggccgaggt 480
gatagtgtgg tttatggact gaggtcaaaa tctaagaagt ttcgcagacc tgacatccag 540
taccetgatg ctacagacga gcacatcace tcacacatgg aaagcgagga gttgaatggt 600
gcatacaagg ccatccccgt tgcccaggac ctgaacgcgc cttctgattg ggacagccgt 660
gggaaggaca gttatgaaac gagtcagctg gatgaccaga gtgctgaagc ccacagccac 720
aagcagtcca gattatataa geggaaagct aatgatgaga geaatgagca tteegatgtg 780
attgatagtc aggaactttc caaagtcagc cgtgaattcc acagccatqa atttcacagc 840
catgaagata tgctggttgt agaccccaaa agtaaggaag aagataaaca cctgaaattt 900
cgtatttctc atgaattaga tagtgcatct tctgaggtca at
<210> 172
<211> 314
<212> PRT
<213> Homo sapiens
<400> 172
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Ile Pro Val Lys Gln Ala Asp Ser Gly Ser Ser Glu Glu Lys Gln Leu
Tyr Asn Lys Tyr Pro Asp Ala Val Ala Thr Trp Leu Asn Pro Asp Pro
Ser Gln Lys Gln Asn Leu Leu Ala Pro Gln Asn Ala Val Ser Ser Glu
Glu Thr Asn Asp Phe Lys Gln Glu Thr Leu Pro Ser Lys Ser Asn Glu
                    70
                                        75
Ser His Asp His Met Asp Asp Met Asp Asp Glu Asp Asp Asp His
                                    90
Val Asp Ser Gln Asp Ser Ile Asp Ser Asn Asp Ser Asp Val Asp
                                105
Asp Thr Asp Asp Ser His Gln Ser Asp Glu Ser His His Ser Asp Glu
                            120
                                                125
Ser Asp Glu Leu Val Thr Asp Phe Pro Thr Asp Leu Pro Ala Thr Glu
                        135
                                            140
Val Phe Thr Pro Val Val Pro Thr Val Asp Thr Tyr Asp Gly Arg Gly
                    150
                                        155
                                                            160
Asp Ser Val Val Tyr Gly Leu Arg Ser Lys Ser Lys Lys Phe Arg Arg
                165
                                    170
                                                        175
Pro Asp Ile Gln Tyr Pro Asp Ala Thr Asp Glu His Ile Thr Ser His
                                185
                                                    190
Met Glu Ser Glu Glu Leu Asn Gly Ala Tyr Lys Ala Ile Pro Val Ala
                            200
Gln Asp Leu Asn Ala Pro Ser Asp Trp Asp Ser Arg Gly Lys Asp Ser
                        215
                                            220
Tyr Glu Thr Ser Gln Leu Asp Asp Gln Ser Ala Glu Ala His Ser His
                    230
Lys Gln Ser Arg Leu Tyr Lys Arg Lys Ala Asn Asp Glu Ser Asn Glu
                                    250
His Ser Asp Val Ile Asp Ser Gln Glu Leu Ser Lys Val Ser Arg Glu
            260
                                265
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Phe His Ser His Glu Phe His Ser His Glu Asp Met Leu Val Val Asp 275 280

Pro Lys Ser Lys Glu Glu Asp Lys His Leu Lys Phe Arg Ile Ser His 295 300

Glu Leu Asp Ser Ala Ser Ser Glu Val Asn 310

<210> 173

<211> 1524

<212> DNA

<213> Homo sapiens

<400> 173

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<210> 174

<211> 300

<212> PRT

<213> Homo sapiens

<400> 174

Met Arg Ile Ala Val Ile Cys Phe Cys Leu Leu Gly Ile Thr Cys Ala Ile Pro Val Lys Gln Ala Asp Ser Gly Ser Ser Glu Glu Lys Gln Leu 25 Tyr Asn Lys Tyr Pro Asp Ala Val Ala Thr Trp Leu Asn Pro Asp Pro 40 Ser Gln Lys Gln Asn Leu Leu Ala Pro Gln Thr Leu Pro Ser Lys Ser 55 Asn Glu Ser His Asp His Met Asp Asp Met Asp Asp Glu Asp Asp Asp 70 75

Asp His Val Asp Ser Gln Asp Ser Ile Asp Ser Asn Asp Ser Asp Asp 90

Val Asp Asp Thr Asp Asp Ser His Gln Ser Asp Glu Ser His His Ser

100 105

Asp Glu Ser Asp Glu Leu Val Thr Asp Phe Pro Thr Asp Leu Pro Ala 120 125

Thr Glu Val Phe Thr Pro Val Val Pro Thr Val Asp Thr Tyr Asp Gly 135

Arg Gly Asp Ser Val Val Tyr Gly Leu Arg Ser Lys Ser Lys Lys Phe 150 155

Arg Arg Pro Asp Ile Gln Tyr Pro Asp Ala Thr Asp Glu Asp Ile Thr 170 175

Ser His Met Glu Ser Glu Glu Leu Asn Gly Ala Tyr Lys Ala Ile Pro 185 190

Val Ala Gln Asp Leu Asn Ala Pro Ser Asp Trp Asp Ser Arg Gly Lys 200 205

Asp Ser Tyr Glu Thr Ser Gln Leu Asp Asp Gln Ser Ala Glu Thr His 215 220

Ser His Lys Gln Ser Arg Leu Tyr Lys Arg Lys Ala Asn Asp Glu Ser 230 235

Asn Glu His Ser Asp Val Ile Asp Ser Gln Glu Leu Ser Lys Val Ser 245 250 255

Arg Glu Phe His Ser His Glu Phe His Ser His Glu Asp Met Leu Val 260 265 270

Val Asp Pro Lys Ser Lys Glu Glu Asp Lys His Leu Lys Phe Arg Ile 275 280 285

Ser His Glu Leu Asp Ser Ala Ser Ser Glu Val Asn 290 295

<210> 175

<211> 861

<212> DNA

<213> Homo sapiens

<400> 175

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<210> 176

<211> 287

<212> PRT

<213> Homo sapiens

<400> 176

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                                25
Ala Val Ser Ser Glu Glu Thr Asn Asp Phe Lys Gln Glu Thr Leu Pro
                            40
Ser Lys Ser Asn Glu Ser His Asp His Met Asp Asp Met Asp Asp Glu
                        55
Asp Asp Asp His Val Asp Ser Gln Asp Ser Ile Asp Ser Asn Asp
                    70
Ser Asp Asp Val Asp Asp Thr Asp Asp Ser His Gln Ser Asp Glu Ser
                                    90
His His Ser Asp Glu Ser Asp Glu Leu Val Thr Asp Phe Pro Thr Asp
            100
                                105
                                                     110
Leu Pro Ala Thr Glu Val Phe Thr Pro Val Val Pro Thr Val Asp Thr
        115
                            120
                                                125
Tyr Asp Gly Arg Gly Asp Ser Val Val Tyr Gly Leu Arg Ser Lys Ser
                        135
                                            140
Lys Lys Phe Arg Arg Pro Asp Ile Gln Tyr Pro Asp Ala Thr Asp Glu
                    150
                                        155
His Ile Thr Ser His Met Glu Ser Glu Glu Leu Asn Gly Ala Tyr Lys
                165
                                    170
                                                         175
Ala Ile Pro Val Ala Gln Asp Leu Asn Ala Pro Ser Asp Trp Asp Ser
            180
                                185
                                                     1.90
Arg Gly Lys Asp Ser Tyr Glu Thr Ser Gln Leu Asp Asp Gln Ser Ala
                            200
                                                 205
Glu Ala His Ser His Lys Gln Ser Arg Leu Tyr Lys Arg Lys Ala Asn
                        215
                                            220
Asp Glu Ser Asn Glu His Ser Asp Val Ile Asp Ser Gln Glu Leu Ser
                    230
                                        235
Lys Val Ser Arg Glu Phe His Ser His Glu Phe His Ser His Glu Asp
                245
                                    250
Met Leu Val Val Asp Pro Lys Ser Lys Glu Glu Asp Lys His Leu Lys
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Phe Arg Ile Ser His Glu Leu Asp Ser Ala Ser Ser Glu Val Asn
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<210> 177
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<400> 177

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<211> 3213

<212> DNA

<213> Homo sapiens

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tgaggccaga tggagaatac actttgctgg cacctgtgaa taatgcattt tctgatgata 1260
ctctcagcat ggttcagcgc ctccttaaat taattctgca gaatcacata ttgaaaqtaa 1320
aagttggcct taatgagctt tacaacgggc aaatactgga aaccatcgga ggcaaacagc 1380
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gtaagcaagg gagaaacggt gcgattcaca tattccgcga gatcatcaag ccagcagaga 1500
aatccctcca tgaaaagtta aaacaagata agcgctttag caccttcctc agcctacttg 1560
aagctgcaga cttgaaagag ctcctgacac aacctggaga ctggacatta tttgtgccaa 1620
ccaatgatgc ttttaaggga atgactagtg aagaaaaaga aattctgata cgggacaaaa 1680
atgctcttca aaacatcatt ctttatcacc tgacaccagg agttttcatt ggaaaaggat 1740
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aagtaaatga tacacttctg gtgaatgaat tgaaatcaaa agaatctgac atcatgacaa 1860
caaatggtgt aattcatgtt gtagataaac teetetatee ageagaeaca eetgttggaa 1920
atgatcaact gctggaaata cttaataaat taatcaaata catccaaatt aagtttgttc 1980
gtggtagcac cttcaaagaa atccccgtga ctgtctatac aactaaaatt ataaccaaag 2040
ttgtggaacc aaaaattaaa gtgattgaag gcagtcttca gcctattatc aaaactgaag 2100
gacccacact aacaaaagtc aaaattgaag gtgaacctga attcagactg attaaagaag 2160
gtgaaacaat aactgaagtg atccatggag agccaattat taaaaaaatac accaaaatca 2220
ttgatggagt gcctgtggaa ataactgaaa aagagacacq agaagaacqa atcattacaq 2280
gtcctgaaat aaaatacact aggatttcta ctggaggtgg agaaacagaa gaaactctga 2340
agaaattgtt acaagaagag gtcaccaagg tcaccaaatt cattgaaggt ggtgatggtc 2400
atttatttga agatgaagaa attaaaagac tgcttcaggg agacacaccc gtgaggaagt 2460
tgcaagccaa caaaaaagtt caaggttcta gaagacgatt aagggaaggt cgttctcagt 2520
gaaaatccaa aaaccagaaa aaaatgttta tacaacccta agtcaataac ctgaccttag 2580
aaaattgtga gagccaagtt gacttcagga actgaaacat cagcacaaag aagcaatcat 2640
caaataattc tgaacacaaa tttaatattt ttttttctga atgagaaaca tgagggaaat 2700
tgtggagtta gcctcctgtg gtaaaggaat tgaagaaaat ataacacctt acaccctttt 2760
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Lys Lys Ser Ile Cys Gly Gln Lys Thr Thr Val Leu Tyr Glu Cys Cys
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Ala	Arg 210	Ile	Ile	His	Gly	Asn 215	Gln	Ile	Ala	Thr	Asn 220	Gly	Val	Val	His
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<213> Homo sapiens

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135

150

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155

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attocatgaa tgtatcagga aatatatatg tgtgtgtatg tttgcacact tgttgtgtgg 1920
gctgtgagtg taagtgtgag taagagctgg tgtctgattg ttaagtctaa atatttcctt 1980
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atcocttcct tttagcctag ttcatccaat cctcactggg tggggtgagg accactcctt 2220
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atcaataaaa tgtgattttt ctga
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<213> Homo sapiens
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                                 25
Cys Leu Asn Gly Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile
                             40
His Trp Cys Asn Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile
                        55
Asp Lys Ser Lys Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly
                    70
                                         75
Lys Ala Ser Thr Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser
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Gln Leu Gly Leu Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg
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Arg Arg Pro Trp Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln
                   135
Glu Cys Met Val His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro
                150
                                 155
Pro Glu Glu Leu Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg
             165
                              170
Phe Lys Ile Ile Gly Gly Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp
                          185
Phe Ala Ala Ile Tyr Arg Arg His Arg Gly Gly Ser Val Thr Tyr Val
                       200
Cys Gly Gly Ser Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His
                    215
                                     220
Cys Phe Ile Asp Tyr Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly
              230
                                 235
Arg Ser Arg Leu Asn Ser Asn Thr Gln Gly Glu Met Lys Phe Glu Val
                              250
Glu Asn Leu Ile Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His
                          265
His Asn Asp Ile Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys
  275 280
Ala Gln Pro Ser Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr
                    295
Asn Asp Pro Gln Phe Gly Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys
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Glu Asn Ser Thr Asp Tyr Leu Tyr Pro Glu Gln Leu Lys Met. Thr Val
             325 330
Val Lys Leu Ile Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly
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Ser Glu Val Thr Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Lys
    355 360
Thr Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu
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                                    380
Gln Gly Arg Met Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys
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                     395
Ala Leu Lys Asp Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu
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<210> 185
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<400> 185

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gccggggtcc	ccggagttgc	agctcccgga	gctccggcgg	cggctccacc	ggcgaaagag	180
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atggaaatat	ccattcaccg	cagcctcgcc	caccagcacg	tcgtaggatt	ccacggcttt	420
ttcgaggaca	acgacttcgt	gttcgtggtg	ttggagctct	gccgccggag	gtctctcctg	480
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<211> 2123

<212> DNA

<213> Homo sapiens

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<210> 186

<211> 603

<212> PRT

<213> Homo sapiens

<400> 186

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		195					200					205			
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Lys 225	Lys	Glu	His	Ser	Phe 230	Glu	Val	Asp	Val	Trp 235	Ser	Ile	Gly	Cys	Ile 240
Met	Tyr	Thr	Leu	Leu 245	Val	Gly	Lys	Pro	Pro 250	Phe	Glu	Thr	Ser	Cys 255	Leu
	Glu		260					265					270		_
	Ile	275					280					285			
Asp	Pro 290	Thr	Ala	Arg	Pro	Thr 295	Ile	Asn	Glu	Leu	Leu 300	Asn	Asp	Glu	Phe
Phe 305	Thr	Ser	Gly	Tyr	Ile 310	Pro	Ala	Arg	Leu	Pro 315	Ile	Thr	Cys	Leu	Thr 320
	Pro			325					330			_		335	
Arg	Lys	Pro	Leu 340	Thr	Val	Leu	Asn	Lys 345	Gly	Leu	Glu	Asn	Pro 350	Leu	Pro
Glu	Arg	Pro 355	Arg	Glu	Lys	Glu	Glu 360	Pro	Val	Val	Arg	Glu 365	Thr	Gly	Glu
	Val 370				,	375					380				
Asn 385	Ala	Ser	Lys	Pro	Ser 390	Glu	Arg	Gly	Leu	Val 395	Arg	Gln	Glu	Glu	Ala 400
	Asp			405					410				_	415	_
	Ser		420					425					430		
	Val	435					440					445			
	Ser 450					455					460		_		
465	Ser				470					475					480
	Phe			485					490		_		_	495	
	Thr		500					505					510		
	Trp	515					520					525			_
	Val 530					535					540				
545	Leu				550					555					560
	Tyr			565					570	_	_		_	575	
	Ser		580					585			Asp	Lys	Leu 590	Leu	Ser
Ser	Arg	Ser 595	Ala	Ser	Asn	Arg	Leu 600	Lys	Ala	Ser					

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<210> 187 <211> 2617

<212> DNA

<213> Homo sapiens

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<213> Homo sapiens

<400> 188

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 Leu
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 Glu
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 Leu
 Glu
 Lys
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 Lys

 Glu
 Ser
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 Asn
 Val
 Asp
 Glu
 Asn
 Ile
 Arg
 Lys
 Leu
 Thr
 Gly
 Arg

 Asp
 Pro
 Asp
 Pro
 Ile
 Gln
 Ala
 Arg
 Leu
 Ala
 Leu
 Ala
 Leu
 Ser

 Gly
 Pro
 Gly
 Arg
 Gly
 Arg
 Gly
 Ser
 Leu
 Leu
 Leu
 Arg
 Arg
 Gly

Phe 65	Ser	Asp	Ser	Gly	Gly 70	Pro	Pro	Ala	Lys	Gln 75	Arg	Asp	Leu	Glu	Gly 80
Ala	Val	Ser	Arg	Leu 85	Gly	Gly	Glu	Arg	Arg 90	Thr	Arg	Arg	Glu	Ser 95	Arg
Gln	Glu	Ser	Asp 100	Pro	Glu	Asp	Asp	Asp 105	Val	Lys	Lys	Pro	Ala 110	Leu	Gln
Ser	Ser	Val 115	Val	Ala	Thr	Ser	Lys 120	Glu	Arg	Thr	Arg	Arg 125	Asp	Leu	Ile
Gln	Asp 130	Gln	Asn	Met	Asp	Glu 135	Lys	Gly	Lys	Gln	Arg 140	Asn	Arg	Arg	Ile
Phe 145	Gly	Leu	Leu	Met	Gly 150	Thr	Leu	Gln	Lys	Phe 155	Lys	Gln	Glu	Ser	Thr 160
Val	Ala	Thr	Glu	Arg 165	Gln	Asn	Arg	Arg	Gln 170	Glu	Ile	Glu	Gln	Lys 175	Leu
Glu	Val	Gln	Ala 180	Glu	Glu	Glu	Arg	Lys 185	Gln	Val	Glu	Asn	Glu 190	Arg	Arg
		195			Arg	_	200					205			
	210				Leu	215					220				
225					Lys 230					235					240
				245	Arg				250			-		255	
Glu	Ser	Gln	Arg 260	Lys	Met	Asn	Ala	Leu 265	Phe	Asp	Gly	Arg	Arg 270	Ile	Glu
		275			Asn	_	280			_		285			
	290				His	295					300				
305					Lys 310					315					320
	_			325	Asn	_			330					335	
			340		Gly			345		_			350		
		355			Lys		360					365			
	370				Ser	375				-	380				
385		_			Glu 390					395	_				400
				405	Glu				410					415	
			420		Lys			425					430		
		435	_		Cys	-	440					$4\overline{4}5$			
	450				Glu	455					460				
465					Glu 470					475					480
				485	Gln				490					495	
			500		Pro			505					510		
		515			Ala		520					525			
Glu	Asp	Leu	Ser	Leu	Ala	Val	Leu	Gln	Pro	Thr	Pro	Gln	Val	Thr	Gln

 Glu His Gly His Phe Leu Pro Slu Arg Lys Asp Phe Pro Val Glu Ser 545
 Ser 550
 Ser 560
 Ser 560
 Ser 570
 Ser 570

595 600 605

Ser Ser Ser Ser Ser Thr Ser Ser Ser Ser Gly Ser Ser Ser Ser Ser Ser 610 615 620

Gly Ser Ser Ser Ser Arg Ser Ser Ser Ser Ser Ser Ser Thr Ser 625 630 635 640

Gly Ser Ser Ser Ser Arg Asp Ser Ser Ser Ser Ser Ser Ser Ser Glu

645 650 655

Ser Arg Ser Arg Gly Arg Gly His Asn Arg Asp Arg Lys His

660 665 670

Arg Arg Ser Val Asp Arg Lys Arg Arg Asp Thr Ser Gly Leu Glu Arg 675 680 685

Ser His Lys Ser Ser Lys Gly Gly Ser Ser Arg Asp Thr Lys Gly Ser

690
695
700
Lys Asp Lys Asn Ser Arg Ser Asp Arg Lys Arg Ser Ile Ser Glu Ser
705
710
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705 710 715 720 Ser Arg Ser Gly Lys Arg Ser Ser Arg Ser Glu Arg Asp Arg Lys Ser 725 730 735

Asp Arg Lys Asp Lys Arg Arg 740

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<211> 1182

<212> DNA

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<211> 158

<212> PRT

<213> Homo sapiens

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<210> 191

<211> 1595

<212> DNA

<213> Homo sapiens

<400> 191

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<211> 175
<212> PRT
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Arg Leu Lys Arg Ala Val Ser Glu His Gln Leu Leu His Asp Lys Gly
                            40
Lys Ser Ile Gln Asp Leu Arg Arg Phe Phe Leu His His Leu Ile
Ala Glu Ile His Thr Ala Glu Ile Arg Ala Thr Ser Glu Val Ser Pro
                    70
                                        75
Asn Ser Lys Pro Ser Pro Asn Thr Lys Asn His Pro Val Arg Phe Gly
                85
                                    90
Ser Asp Asp Glu Gly Arg Tyr Leu Thr Gln Glu Thr Asn Lys Val Glu
                                105
Thr Tyr Lys Glu Gln Pro Leu Lys Thr Pro Gly Lys Lys Lys Gly
                            120
lys Pro Gly Lys Arg Lys Glu Gln Glu Lys Lys Lys Arg Arg Thr Arg
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<211> 168

<212> PRT

<213> Homo sapiens

<400> 194

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<211> 890 <212> PRT

<213> Homo sapiens

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				645	Glu				650					655	
			660		Ser			665					670		
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705					Leu 710		_	_		715					720
				725	Phe				730					735	
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		755			Ala		760					765			
	770				Ala	775					780				-
785					Ala 790					795					800
				805	Lys				810					815	
			820		Gly			825			-		830		
		835			Gln		840					845			
	850				Leu	855					860				
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Val Ile His Leu Ala Pro Pro Ser Glu Tyr Pro Gly Ala Gly Ser Ser
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Ser Val Phe Ser Val Leu Ser Asn Ser Ala Glu Val Lys Arg Gly Arg
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Leu Glu Asp Val Val Gly Gly Cys Cys Tyr Arg Val Asn Asn Ser Leu
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Asp His Glu Tyr Gln Pro Arg Pro Val Glu Val Ile Ile Ser Ser Ala
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Lys Glu Met Val Gly Gln Lys Met Lys Tyr Ser Ile Val Ser Arg Asn
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                                105
                                                    110
Cys Glu His Phe Val Ala Gln Leu Arg Tyr Gly Lys Ser Arg Cys Lys
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                            120
                                                125
Gln Val Glu Lys Ala Lys Val Glu Val Gly Val Ala Thr Ala Leu Gly
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His Met Ile Ile Arg Thr Leu Ser Thr Phe Arg Asn Tyr Ile Met Asp
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Phe Gln Val Gly Lys Glu Phe Glu Glu Asp Leu Thr Gly Ile Asp Asp
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Arg Lys Cys Met Thr Thr Val Ser Trp Asp Gly Asp Lys Leu Gln Cys
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Val Gln Lys Gly Glu Lys Glu Gly Arg Gly Trp Thr Gln Trp Ile Glu
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<213> Homo sapiens

<400> 202

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269

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5 10 His Lys Tyr Ser Cys Gln Glu Gly Asp Lys Phe Lys Leu Ser Lys Gly Glu Met Lys Glu Leu Leu His Lys Glu Leu Pro Ser Phe Val Gly Glu 40 Lys Val Asp Glu Glu Gly Leu Lys Lys Leu Met Gly Ser Leu Asp Glu 55 Asn Ser Asp Gln Gln Val Asp Phe Gln Glu Tyr Ala Val Phe Leu Ala 70 75 Leu Ile Thr Val Met Cys Asn Asp Phe Phe Gln Gly Cys Pro Asp Arg 90 Pro

<210> 207 <211> 799

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<213> Homo sapiens

<400> 207

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<210> 208

<211> 96

<212> PRT

<213> Homo sapiens

<400> 208

Met Cys Cys Thr Lys Ser Leu Leu Leu Ala Ala Leu Met Ser Val Leu Leu Leu His Leu Cys Gly Glu Ser Glu Ala Ala Ser Asn Phe Asp Cys 25 Cys Leu Gly Tyr Thr Asp Arg Ile Leu His Pro Lys Phe Ile Val Gly Phe Thr Arg Gln Leu Ala Asn Glu Gly Cys Asp Ile Asn Ala Ile Ile 55 Phe His Thr Lys Lys Leu Ser Val Cys Ala Asn Pro Lys Gln Thr 70 Trp Val Lys Tyr Ile Val Arg Leu Leu Ser Lys Lys Val Lys Asn Met 90

<210> 209

<211> 2133

<212> DNA

<213> Homo sapiens

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<211> 303

<212> PRT

<213> Homo sapiens

<400> 210

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 Pro
 Gln
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 Glu
 Ala
 Leu
 Pro
 Asp
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 Thr
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 Val
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 Asp

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100
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Ser Asn Asp Asn Lys Thr Phe Asp Ser Ser Cys His Phe Phe Ala Thr
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                                                 125
Lys Cys Thr Leu Glu Gly Thr Lys Lys Gly His Lys Leu His Leu Asp
                        135
                                             140
Tyr Ile Gly Pro Cys Lys Tyr Ile Pro Pro Cys Leu Asp Ser Glu Leu
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                                         155
Thr Glu Phe Pro Leu Arg Met Arg Asp Trp Leu Lys Asn Val Leu Val
                                    170
                                                         175
Thr Leu Tyr Glu Arg Asp Glu Asp Asn Asn Leu Leu Thr Glu Lys Gln
                                185
                                                     190
Lys Leu Arg Val Lys Lys Ile His Glu Asn Glu Lys Arg Leu Glu Ala
        195
                            200
                                                 205
Gly Asp His Pro Val Glu Leu Leu Ala Arg Asp Phe Glu Lys Asn Tyr
                        215
                                             220
Asn Met Tyr Ile Phe Pro Val His Trp Gln Phe Gly Gln Leu Asp Gln
                    230
                                         235
His Pro Ile Asp Gly Tyr Leu Ser His Thr Glu Leu Ala Pro Leu Arg
                245
                                    250
Ala Pro Leu Ile Pro Met Glu His Cys Thr Thr Arg Phe Phe Glu Thr
            260
                                265
Cys Asp Leu Asp Asn Asp Lys Tyr Ile Ala Leu Asp Glu Trp Ala Gly
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Cys Phe Gly Ile Lys Gln Lys Asp Ile Asp Lys Asp Leu Val Ile
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<210> 211

<211> 2228

<212> DNA

<213> Homo sapiens

<400> 211

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<211> 471

<212> PRT

<213> Homo sapiens

<400> 212

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 Pro His Ser Ser Asp Thr Glu Leu Pro Lys Asp Lys Leu Ser Ser Ala

 325
 330
 335

 Asp Asp His Arg Val Asn Ser Gly Phe Gly Arg Gly Leu Ser Asp Lys
 340
 350

 340
 345
 350

Lys Ser Gly Glu Ser Gln Val Leu Phe Glu Thr Glu Ile Ser Arg Lys 355 360 365

Leu Phe Asp Thr Leu Asn Glu Asp Leu Phe Gln Lys Ile Leu Val Pro 370 375 380

Ile Gln Gln Val Leu Lys Glu Gly His Leu Glu Lys Thr Glu Ile Asp 385 390 395 400

Glu Val Val Leu Val Gly Gly Ser Thr Arg Ile Pro Arg Ile Arg Gln
405 410 415

Val Ile Gln Glu Phe Phe Gly Lys Asp Pro Asn Thr Ser Val Asp Pro 420 425 430

Asp Leu Ala Val Val Thr Gly Val Ala Ile Gln Ala Gly Ile Asp Gly 435 440 445

Gly Ser Trp Pro Leu Gln Val Ser Ala Leu Glu Ile Pro Asn Lys His 450 455 460

Leu Gln Lys Thr Asn Phe Asn 465 470

<210> 213

<211> 1224

<212> DNA

<213> Homo sapiens

<400> 213

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<210> 214

<211> 344

<212> PRT

<213> Homo sapiens

<400> 214

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Ala Pro Ser Gly Leu Ser Thr Leu Pro Gln Arg Val Leu Arg Lys Glu

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Pro Thr Ala Ala Pro Gly Gln Lys Val Met Glu Asn Ser Ser Gly Thr
Pro Asp Ile Leu Thr Arg His Phe Thr Ile Asp Asp Phe Glu Ile Gly
                                        75
Arg Pro Leu Gly Lys Gly Lys Phe Gly Asn Val Tyr Leu Ala Arg Glu
                                    90
Lys Lys Ser His Phe Ile Val Ala Leu Lys Val Leu Phe Lys Ser Gln
                                105
                                                    110
Ile Glu Lys Glu Gly Val Glu His Gln Leu Arg Arg Glu Ile Glu Ile
        115
                            120
                                                125
Gln Ala His Leu His His Pro Asn Ile Leu Arg Leu Tyr Asn Tyr Phe
                        135
                                            140
Tyr Asp Arg Arg Ile Tyr Leu Ile Leu Glu Tyr Ala Pro Arg Gly
                    1.50
                                        155
Glu Leu Tyr Lys Glu Leu Gln Lys Ser Cys Thr Phe Asp Glu Gln Arg
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                                    170
Thr Ala Thr Ile Met Glu Glu Leu Ala Asp Ala Leu Met Tyr Cys His
                                185
Gly Lys Lys Val Ile His Arg Asp Ile Lys Pro Glu Asn Leu Leu Leu
        195
                            200
                                                205
Gly Leu Lys Gly Glu Leu Lys Ile Ala Asp Phe Gly Trp Ser Val His
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                                            220
Ala Pro Ser Leu Arg Arg Lys Thr Met Cys Gly Thr Leu Asp Tyr Leu
                    230
                                        235
Pro Pro Glu Met Ile Glu Gly Arg Met His Asn Glu Lys Val Asp Leu
                245
                                    250
Trp Cys Ile Gly Val Leu Cys Tyr Glu Leu Leu Val Gly Asn Pro Pro
                                265
Phe Glu Ser Ala Ser His Asn Glu Thr Tyr Arg Arg Ile Val Lys Val
                            280
Asp Leu Lys Phe Pro Ala Ser Val Pro Thr Gly Ala Gln Asp Leu Ile
                       295
                                            300
Ser Lys Leu Leu Arg His Asn Pro Ser Glu Arg Leu Pro Leu Ala Gln
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Val Ser Ala His Pro Trp Val Arg Ala Asn Ser Arg Arg Val Leu Pro
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Pro Ser Ala Leu Gln Ser Val Ala
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<210> 215 <211> 1421

<212> DNA

<213> Homo sapiens

<400> 215

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<210> 216 <211> 234 <212> PRT

<213> Homo sapiens

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Pro Glu Gly Pro Ala Val Ala Val Arg Leu Ser Lys Asp Arg Ser Thr
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Asp Asn Phe Thr Glu Ala Leu Ala Glu Thr Ala Cys Arg Gln Met Gly
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Tyr Ser Ser Lys Pro Thr Phe Arg Ala Val Glu Ile Gly Pro Asp Gln
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<212> PRT

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<400> 222

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Trp	Pro	Ser	Leu	Leu 565	Arg	His	Arg	Phe	Leu 570	Glu	Glu	Phe	Ile	Thr 575	Pro
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	930		Thr			935					940				
945			Glu		950					955					960
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Glu 118	Lys 5	Gln	Asp	Glu	Gln 1190		Gly	Leu	Pro	Gly 119		Gly	Gly	Lys	Ala 1200
Lys	Gly	Lys	Lys	Thr 1205		Met	Ala	Glu	Val 121		Pro	Ser	Pro	Arg 1215	_
Gln	Arg	Val	11e 122		Arg	Ile	Thr	Ile 1225		Met	Lys	Ala	Glu 1230		Glu
Lys	Lys	Asn 123		Lys	Lys	Ile	Lys 1240		Glu	Asn	Thr	Glu 1245		Ser	Pro
Gln	Glu 1250		Gly	Val	Glu	Leu 125		Gly	Leu	Lys	Gln 1260	_	Leu	Glu	Lys
Lys 126	Gln 5	Lys	Arg	Glu	Pro 1270		Thr	Lys	Thr	Lys 1275		Gln	Thr	Thr	Leu 1280
Ala	Phe	Lys	Pro	Ile 1285	-	Lys	Gly	Lys	Lys 1290		Asn	Pro	Trp	Pro 1295	_
Ser	Glu	Ser	Asp 130	_	Ser	Ser	Asp	Glu 1305		Asn	Phe	Asp	Val 1310		Pro
Arg	Glu	Thr 131		Pro	Arg	Arg	Ala 1320		Thr	Lys	Thr	Lys 1325		Thr	Met
Asp	Leu 1330	_	Ser	Asp	Glu	Asp 1335		Ser	Asp	Phe	Asp 1340		Lys	Thr	Asp
Asp 134	Glu 5	Asp	Phe	Val	Pro 1350		Asp	Ala	Ser	Pro 135		Lys	Thr	Lys	Thr 1360
Ser	Pro	Lys	Leu	Ser 136		Lys	Glu	Leu	Lys 1370		Gln	Lys	Ser	Val 1375	
Ser	Asp	Leu	Glu 138		Asp	Asp	Val	Lys 1385		Ser	Val	Pro	Leu 1390		Ser
Ser	Pro	Pro 139		Thr	His	Phe	Pro 1400	_	Glu	Thr	Glu	Ile 1405		Asn	Pro
Val	Pro 141	Lys		Asn	Val	Thr 141	Val		Lys	Thr	Ala 1420	Ala		Ser	Gln
Ser 142	Ser 5	Thr	Ser	Thr	Thr 1430		Ala	Lys	Lys	Arg 1435		Ala	Pro	Lys	Gly 1440

Thr Lys Arg Asp Pro Ala Leu Asn Ser Gly Val Ser Gln Lys Pro Asp 1445 1450 1455

Pro Ala Lys Thr Lys Asp Arg Lys Arg Lys Pro Ser Thr Ser Asp

Pro Ala Lys Thr Lys Asn Arg Arg Lys Arg Lys Pro Ser Thr Ser Asp 1460 1465 1470

Asp Ser Asp Ser Asn Phe Glu Lys Ile Val Ser Lys Ala Val Thr Ser 1475 1480 1485

Lys Lys Ser Lys Gly Glu Ser Asp Asp Phe His Met Asp Phe Asp Ser 1490 1495 1500

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Tyr Leu Glu Glu Ser Asp Glu Asp Asp Leu Phe 1525 1530

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<211> 284

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<213> Homo sapiens

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 Ser
 Ala
 Glu
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 Ala
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 Ala
 Glu
 Ala
 A

Glu Glu Leu Asp Arg Ala Gln Glu Arg Leu Ala Thr Ala Leu Gln Lys

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Lys Tyr Glu Glu Val Ala Arg Lys Leu Val Ile Ile Glu Ser Asp Leu
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Glu Arg Ala Glu Glu Arg Ala Glu Leu Ser Glu Gly Lys Cys Ala Glu
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                    230
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Phe Ala Glu Arg Ser Val Thr Lys Leu Glu Lys Ser Ile Asp Asp Leu
                245
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Glu Asp Glu Leu Tyr Ala Gln Lys Leu Lys Tyr Lys Ala Ile Ser Glu
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Tyr Ser Asn Val Ile Phe Leu Glu Val Asp Val Asp Cys Gln Asp
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Val Ala Ser Glu Cys Glu Val Lys Cys Thr Pro Thr Phe Gln Phe Phe
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Leu Glu Ala Thr Ile Asn Glu Leu Val 100 105

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<400> 227

<210> 228

<211> 179

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Gln Glu Pro

165

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<211> 777

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Val Leu Leu Gly Ser Lys Ile Leu Lys Pro Arg Arg Ser Leu Ser
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Ser Tyr Gly Ile Asp Lys Glu Lys Thr Ile His Leu Thr Leu Lys Val
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Val Lys Pro Ser Asp Glu Glu Leu Pro Leu Phe Leu Val Glu Ser Gly
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Asp Glu Ala Lys Arg His Leu Leu Gln Val Arg Arg Ser Ser Val
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Ala Gln Val Lys Ala Met Ile Glu Thr Lys Thr Gly Ile Ile Pro Glu
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                                                125
Thr Gln Ile Val Thr Cys Asn Gly Lys Arg Leu Glu Asp Gly Lys Met
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PCT/US02/18638

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Glu Cys Lys Glu Cys Gly Lys Ala Phe Lys Tyr Cys Ser Asn Leu Asn

235

230

245 250 Asp His Gln Arg Ile His Thr Gly Glu Lys Pro Tyr Glu Cys Lys Val 265 Cys Gly Lys Ala Phe Thr Lys Ser Ser Gln Leu Phe Leu His Leu Arg 280 Ile His Thr Gly Glu Lys Pro Tyr Glu Cys Lys Glu Cys Gly Lys Ala 295 Phe Thr Gln His Ser Arg Leu Ile Gln His Gln Arg Met His Thr Gly 310 315 Glu Lys Pro Tyr Glu Cys Lys Gln Cys Gly Lys Ala Phe Asn Ser Ala 325 330 Ser Thr Leu Thr Asn His His Arg Ile His Ala Gly Glu Lys Leu Tyr 340 345 Glu Cys Glu Glu Cys Arg Lys Ala Phe Ile Gln Ser Ser Glu Leu Ile 360 365 Gln His Gln Arg Ile His Thr Asp Glu Lys Pro Tyr Glu Cys Asn Glu 375 380 Cys Gly Lys Ala Phe Asn Lys Gly Ser Asn Leu Thr Arg His Gln Arg 395 390 Ile His Thr Gly Glu Lys Pro Tyr Asp Cys Lys Glu Cys Gly Lys Ala 405 410 Phe Gly Ser Arg Ser Asp Leu Ile Arg His Glu Gly Ile His Thr Gly

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Xaa

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<213> Homo sapiens

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Gln Glu Ala Thr Val Leu Thr Ser His Thr Leu Pro Asp Ser Leu Val
                        375
Tyr Gly Ala Asp Trp Ser Trp Leu Leu Phe Arg Ser Leu Gln Arg Ala
385
                    390
                                        395
Pro Ser Trp Ser Phe Pro Ser Asn Leu Gly Thr Lys Thr Ala Asp Leu
                405
                                    410
Lys Gly Ala Ser Glu Leu Pro Thr Pro Cys His Glu Cys Arg Glu Asp
                                425
                                                     430
Asn Asp Gly Glu Gly His Ala Arg Pro Gln Ser Gly Met Lys Pro Leu
        435
                            440
                                                445
Thr Glu Gly Met Arg Lys Asn Gly Thr Trp Leu Gln Ala Thr Ala Ala
                        455
                                            460
Thr Thr Arg Asp Cys Gly Val Asn Pro Glu Glu Ala Asp Ser Ala Phe
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                                        475
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Glu Trp Glu Gly Asn
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<210> 235 <211> 1614 <212> DNA <213> Homo sapiens

nome sup

<400> 235

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<210> 236 <211> 247

<212> PRT

<213> Homo sapiens

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                            40
Lys Lys Ile Ile Glu Thr Lys Met Leu Met Gly Glu Val Met Arg Glu
                        55
Ala Ala Phe Ser Leu Ala Glu Ala Lys Phe Thr Ala Gly Asp Phe Ser
                    70
                                        75
Thr Thr Val Ile Gln Asn Val Asn Lys Ala Gln Val Lys Ile Arg Ala
                85
                                    90
Lys Lys Asp Asn Val Ala Gly Val Thr Leu Pro Val Phe Glu His Tyr
                                105
His Glu Gly Thr Asp Ser Tyr Glu Leu Thr Gly Leu Ala Arg Gly Gly
                            120
Glu Gln Leu Ala Lys Leu Lys Arg Asn Tyr Ala Lys Ala Val Glu Leu
                        135
Leu Val Glu Leu Ala Ser Leu Gln Thr Ser Phe Val Thr Leu Asp Glu
                                        155
Ala Ile Lys Ile Thr Asn Arg Arg Val Asn Ala Ile Glu His Val Ile
                165
                                    170
                                                        175
Ile Pro Arg Ile Glu Arg Thr Leu Ala Tyr Ile Ile Thr Glu Leu Asp
                                185
                                                    190
Glu Arg Glu Arg Glu Glu Phe Tyr Arg Leu Lys Lys Ile Gln Glu Lys
                            200
                                                205
Lys Lys Ile Leu Lys Glu Lys Ser Glu Lys Asp Leu Glu Gln Arg Arg
                        215
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Ala Ala Gly Glu Val Leu Glu Pro Ala Asn Leu Leu Ala Glu Glu Lys
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Asp Glu Asp Leu Leu Phe Glu
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<210> 237 <211> 1658 <212> DNA <213> Homo sapiens

<400> 237

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<210> 238

<211> 277

<212> PRT

<213> Homo sapiens

275

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Glu	Leu	Pro 45	Ala	Lys	Ile	Leu	Val 40	Glu	Phe	Val	Val	Asp 45	Ser	Gln	Lys
Lys	Asp 50	Lys	Leu	Leu	Cys	Ser 55	Gln	Leu	Gln	Val	Ala 60	Asp	Phe	Leu	Gln
Asn 65	Ile	Leu	Ala	Gln	Glu 70	Asp	Thr	Ala	Lys	Gly 75	Leu	Asp	Pro	Leu	Ala 80
Ser	Glu	Asp	Thr	Ser 85	Arg	Gln	Lys	Ala	Ile 90	Ala	Ala	Lys	Glu	Gln 95	Trp
			100	Ala		_	_	105					110	•	
Gly	Leu	Thr 115	Lys	Ala	Leu	Thr	Gln 120	Met	Glu	Glu	Ala	Gln 125	Arg	Lys	Arg
Thr	Gln 130	Leu	Arg	Glu	Ala	Phe 135	Glu	Gln	Leu	Gln	Ala 140	Lys	Lys	Gln	Met
145				Arg	150					155	-				160
				Gln 165					170					175	
-			180	Thr				185	_	-			190	_	
		195		Gln			200			-	_	205			_
Tyr	Gln 210	Thr	Phe	Leu	Gln	Leu 215	Leu	Tyr	Thr	Leu	Gln 220	Gly	Lys	Leu	Leu
225				Glu	230					235		_	~	_	240
Gln	Gln	Pro	Thr	Arg 245	Pro	Gln	Glu	Gln	Ser 250	Thr	Gly	Asp	Thr	Met 255	Gly
Arg	Asp	Pro	Gly 260	Val	Ser	Phe	Lys	Ala 265	Val	Gly	Leu	Gln	Pro 270	Ala	Gly
Asp	Val	Asn	Leu	Pro											